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INHERITANCE OF CEREBRAL DYSRHYTHMIA AND EPILEPSY

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Ever since Hippocrates expressed the opinion that epilepsy is a familial disease the inheritance of epilepsy has been a subject for debate. The principal evidence has been gathered from the family histories of persons subject to seizures. The most comprehensive data from extramural patients have been furnished by members of the Association for Research in Nervous and Mental Diseases and the American Neurological Association. The family histories of 2,130 patients have been tabulated by one of us (W.G.L.) and will be presented in detail later. The incidence of seizures among the 13,262 near relatives (parents, siblings and children) of patients in this group is 2.4 per cent. This is approximately five times the incidence of seizures in the general population. However, only 1 in 5 of these patients gives a history of any blood relative affected with seizures. The combined data of Rosanoff, Handy and Rosanoff [1] and of Conrad [2] indicate that if epilepsy is present in one identical twin, it is present in the other in 70 per cent of the cases. On the basis of family histories, some students of the subject assert that epilepsy is a recessive mendelian trait. However, in spite of this statistical evidence, many authorities insist that seizures are wholly and only a symptom of some injury which has been imposed on the central nervous system of a person after his conception. Marchand,[3] in his recent

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1. Rosanoff, A. J.; Handy, L. M., and Rosanoff, I. A.: Etiology of Epilepsy with Special Reference to Its Occurrence in Twins, Arch. Neurol. & Psychiat. **31**:1165 (June) 1934.

2. Conrad, K.: Die Bedeutung der Erbanlage bei der Epilepsie, Deutsche Ztschr. f. Nervenh. **139**:76, 1936.

3. Marchand, L.: Hérédité et épilepsies: Nouvelle revue critique, Paris, 1938, p. 123.

monograph, stated clearly that if intrauterine injuries, injuries occurring at birth, syphilis and such conditions could be done away with epilepsy would be eliminated.

Statistical data of the type mentioned are open to errors due to ignorance or to the withholding of evidence by the informant. There is also disagreement as to whether a history of isolated convulsions in childhood or of fainting should be counted as evidence of epilepsy. For these reasons, a diagnosis of epilepsy based on objective laboratory evidence would be of the greatest help. Even more important (but seemingly visionary) would be the ability to demonstrate a "predisposition" to epilepsy, that quality which has been discussed by writers of all ages but the presence of which, like an unseen planet, could be predicated but not demonstrated. Settlement of the long controversy over the relative influence of heredity and injury of the brain—the significance of "essential" and "symptomatic" epilepsy—has not been possible because the "predisposition" remained hidden in genes and brain tissues. We believe that this mysterious predisposition can now be demonstrated.

Our experience with electroencephalography during the past five years has convinced us that the electrical activity of the cortex represents a constitutional characteristic of the organism and that the electroencephalogram offers a means of studying the hereditary factors of epilepsy. Two opposite characteristics of the electroencephalogram, its variability and its constancy, need to be kept in mind. Unlike some of the genetic traits which have been the object of study in plants and animals, the electrical activity of the brain is fluid and subject to constant change. Besides changing with age, the normal rhythm varies with the activity of the brain, with sleep and attention or with the pulmonary ventilation. On the other hand, the electroencephalogram of a person taken under standard conditions exhibits a certain constancy from day to day and a certain broad individuality. For example, a person with a record characterized by low voltage or by a fast or slow rate tends to have the same type of record when examined repeatedly. The pattern of the normal record is not peculiar to any one person and may be indistinguishable from the record of many other persons. Abnormal records are more bizarre, and when compared with the alternate wave and spike formation of high voltage noted in patients with petit mal, a certain patient's record may be easily distinguished from that of other patients. A collection of 20 such tracings appeared in one of our earlier papers.[4] On the other hand, the constant feature of the record of a patient with various types of seizures may be the inconstancy in

4. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, Arch. Neurol. & Psychiat. **36**:1225 (Dec.) 1936.

the rate or voltage of the waves. In considering the genetic significance of cortical potentials, one should compare them not with finger prints or the color of the eyes but with the facial features. A family resemblance may often be made out; uniovular twins have similar features, though on minute inspection they are never identical. On the other hand, a person may have a "double" who is unrelated. Facial features are subject to both permanent and temporary changes. Voluntary distortions of expression might even be compared to the deceptive artefacts of the electroencephalographic record.

The most conclusive evidence in support of the hypothesis that the electroencephalogram is of genetic value is found in the records of similar twins. Davis and Davis [5] secured tracings from 9 pairs of normal identical twins, and we have records of 7 pairs who had some physical or neurologic abnormality. Six pairs in our series also had cortical dysrhythmia. In each of these 16 pairs of similar twins the two members had similar tracings, whether the tracings were normal or abnormal. In 2 pairs differences in the neurologic and electroencephalographic records of the twins existed, owing to an acquired cerebral lesion in one twin, but a similarity in the basic cortical rhythms was still present. The evidence in the 3 families of twins in which epilepsy was present will be discussed later.

The familial resemblances of normal electroencephalographic records, which Davis and Davis [5] affirmed and Gottlober [6] denied, is difficult to evaluate because of the mixed heritage and the lack of variety in normal tracings. If the electrical rhythm of the cortex is indeed a constitutional characteristic of a person, then abnormal rhythms which are constitutional or hereditary in origin should antedate the onset of seizures and be detectable in the records of a large proportion of persons closely related to the patient. We began three years ago to make electroencephalographic records of the relatives of epileptic patients and of a control group. A preliminary report was given at the meeting of the American Psychiatric Association in June 1938,[7] and a more complete one on 138 relatives before the American Neurological Society in June 1939.[8]

5. Davis, H., and Davis, P. A.: Action Potentials of the Brain in Normal Persons and in Normal States of Cerebral Activity, Arch. Neurol. & Psychiat. **36**:1214 (Dec.) 1936.

6. Gottlober, A. B.: The Inheritance of Brain Potential Patterns, J. Exper. Psychol. **22**:193, 1938.

7. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy, Am. J. Psychiat. **95**:255, 1938.

8. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Inheritance of Epilepsy as Revealed by the Electroencephalograph, J. A. M. A. **113**:1002 (Sept. 9) 1939.

METHOD

Recordings.—The technic of recording is important if the results of various workers are to be compared. Our patients were seated with eyes closed, in an easy chair in a darkened, shielded room, and six electrodes were attached to the scalp, over the two frontal, the two motor and the two occipital areas. These were connected with the grids of six Grass amplifiers, which recorded on six Grass ink writers. Ground electrodes were attached to the lobes of the two ears. Six simultaneous recordings make the detection of transient abnormalities more certain. More important for the purposes of this study, the method permits comparison of the patterns of waves from various cortical areas. Records were taken for at least twenty minutes. Such prolonged observation is important because some patients and some apparently normal subjects have abnormalities which appear only at intervals of many minutes. Account must be taken of the fact that with our methods of making and interpreting records about 3 per cent of patients who are subject to overt seizures have a normal electroencephalographic record. Toward the end of the observation period the subject was asked voluntarily to overventilate his lungs until slow waves of high voltage appeared on the record or until he experienced symptoms which prevented his continuing.

If cortical dysrhythmias are to be found in the symptomless relatives of epileptic patients, persons who are classed as normal might be expected to show similar abnormalities, though not so frequently. The composition of the control group is obviously of great importance. The records of the relatives of epileptic patients should be contrasted with records of the parents, siblings and children of patients who do not have a personal or family history of organic neuropsychiatric diseases. An approximation to such a group was obtained by selecting 76 physicians, technicians and medical students and 24 students from a private boys' school. The immediate family histories of all these were free of epilepsy.

In order to equalize the two groups, the control group should have had more persons above the age of 40 and more married couples. The possible importance of these factors will be discussed later.

Interpretation of Records.—Perhaps the most important point in technic is the interpretation of records. An exact graphic method of reading and comparing records is now available in the frequency analyzer developed by Grass and Gibbs.[9] Data based on this method of examining the records of relatives will be presented later. There is no rule of thumb criterion for judging whether a given electroencephalogram is normal. Interpretation, as in roentgenographic work, requires considerable experience in viewing records of both normal and abnormal persons. As in recognizing a person by his features, inspection of the whole record may be more important than meticulous measurement of a single portion. The whole record must be viewed, the many features of it evaluated and the whole weighed. The person (E. L. G.) who classified these records has had five years of experience, during which tracings of more than 2,000 persons with or without neuropsychiatric symptoms have been studied.

In judging the normality or abnormality of a record, at least three factors are taken into account: (*1*) the dominant frequency, (*2*) the constancy of the record and (*3*) the voltage. By dominant frequency is meant that frequency which appears from inspection of the record to be most continuously present. Sometimes, of course, it is impossible to see a dominant frequency; the record looks

9. Grass, A. M., and Gibbs, F. A.: The Fourier Transform of the Electroencephalogram, J. Neurophysiol. **1**:521, 1938.

like a confused mixture of many frequencies. If there is a dominant frequency and this frequency is slower than 8 per second, the record is considered abnormal, provided the subject is more than 12 years of age. If the dominant frequency is above 25 per second, the record is considered abnormal (no such record occurred in the present series). A dominant frequency below 6 per second is considered abnormal for children between 11 and 15 years of age. Dominant frequencies are not considered abnormal for persons below 5 years of age unless they are of high voltage and from 2 to 3 per second or are faster than 13 per second. At times, in a record which has a normal dominant frequency there may be bursts of two or more abnormal waves, with a frequency of less than 8 or more than 25 per second and a higher voltage than the rest of the record. The larger the number of these abnormal waves during the period of observation, the more sudden the shift from a normal to an abnormal frequency; and the higher the voltage of these abnormal waves, the greater the degree of abnormality of the record. A burst of waves faster than 13 per second which increases from low to high voltage (over 50 microvolts) in several seconds, or a run of square-topped, 4 per second and high voltage, 6 per second waves not accompanied by symptoms is considered evidence of subclinical grand mal or psychomotor seizures. The finding of any of these formations makes the record abnormal. Runs of 3 per second, alternate wave and spike formations are considered diagnostic of petit mal. Changes in rhythm which appear after overventilation are not counted as abnormal unless they form the typical petit mal pattern. Attacks of petit mal lasting less than three seconds are usually subclinical, i. e., are not accompanied by symptoms. The finding of one clearly defined approximately 3 per second, alternate wave and spike formation makes the record abnormal. Elements which weigh in favor of a normal record are the presence of a regular 9 or 10 per second rhythm in the occipital or other leads and the absence of sudden shifts in frequency.

The degree of abnormality was indicated roughly by grading from 1 to 4. For the purposes of this paper, however, records were classified simply as normal, questionable and abnormal. They were read individually during the course of the study and again when the series was completed. The final reading resulted in changing the classification in 10 per cent of the cases.

In addition to inherent abnormalities, the persons who take and who read the record need to keep constantly on the alert for artefacts—"noise" in an amplifier, poor contact of an electrode, sweating or muscular movements of the patient, movement of others in the room, friction of the rubber cushion or tubing and interference from electrical apparatus in the vicinity.

Subjects.—The patients were mostly private patients coming to us or to our colleagues at the Boston City Hospital. A few were charity patients of the hospital. Only 10 patients showed obvious mental deterioration. This point needs emphasis, because the deteriorated institutional patients whose records were examined by Stein[10] had a history of epilepsy in 3.7 per cent of the near relatives. This is 54 per cent greater than the incidence among relatives of the extramural group tabulated by us. Moreover, in our extramural group the incidence of epilepsy among relatives was higher if the patient was mentally deteriorated than if he was mentally normal. Electrical observations were confined to the near relatives (the parents, siblings or children) of patients in order to avoid the uncertainties of mixed heredity which would result if more distant relatives were included.

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10. Stein, C.: Hereditary Factors in Epilepsy: A Comparative Study of 1,000 Institutionalized Epileptics and 1,115 Non-Epileptic Controls, Am. J. Psychiat. **12**:989, 1933.

Of the 94 patients whose relatives were examined, the electrical records of 4 were not secured and the records of 2 (2.2 per cent) were normal. One of these patients with normal records had had only a few convulsions, and the other had been free of symptoms for seventeen years. The number of relatives tested was 183, of whom 143 were parents, 36 were siblings and 4 were children. Seventy-eight per cent of the subjects were parents, since parents were more likely than siblings to accompany patients coming from a distance and it was easier to get records of both parents of a patient than of all of his siblings. Except for the elimination of identical twins when both had seizures, there was no selection of cases on our part. There was some selection on the part of the relatives, for not all of the parents approached were willing to undergo the test. There is evidence, mentioned later, that the relatives whose records could not be obtained would have

Proportion of Near Relatives of Epileptic Patients and of Normal Persons Who Showed Cerebral Dysrhythmia

	Classification of Electroencephalographic Records						
	Number				Percentage		
	Total	Normal	Doubtful	Abnormal	Normal	Doubtful	Abnormal
One parent							
Male	6	3	0	3	50	0	50
Female	27	11	3	13	41	11	48
Total	33	14	3	16	42	10	48
Both parents							
Male	55	20	5	30	36	9	55
Female	55	15	2	38	27	4	69
Total	110	35	7	68	32	6	62
All parents							
Male	61	23	5	33	38	8	54
Female	82	26	5	51	32	6	62
Total	143	49	10	84	34	7	59
Siblings and children							
Male	19	6	3	10	31	16	53
Female	21	4	1	16	19	5	76
Total	40	10	4	26	25	10	65
All relatives							
Male	80	29	8	43	36	10	54
Female	103	30	6	67	29	6	65
Grand total	183	59	14	110	32	8	60
Normal control subjects	100	84	6	10	84	6	10

shown a higher incidence of abnormality. It is important to know whether the heredity in the families selected was unduly great as judged by the usual standards. Of the 183 relatives, 2 had had a single convulsion in childhood and 4 others could be called epileptic, although 3 of these had not experienced seizures for twelve years or more. The occurrence of epilepsy in 4 of the 183 relatives examined is an incidence of 2.2 per cent, which is approximately the same as the incidence (2.4 per cent) among the relatives of the 2,130 patients whose records we have tabulated. In addition, we ascertained that 9.3 per cent of the patients had some near relative and 24 per cent a near or distant relative with a history of seizures. These percentages may be compared with the corresponding values of 12 and 20 per cent, respectively, for the large group.

RESULTS

Of the 183 relatives examined, 60 per cent had definite dysrhythmia and 8 per cent had records which were classed as questionable. Therefore only 32 per cent of these near relatives had electroencephalographic

records which were unmistakably normal. These findings should be compared with the results of examination of the group of 100 normal persons, none of whose near relatives had a history of seizures. In this normal group, 10 (10 per cent) had definitely abnormal records, 6 (6 per cent) questionably abnormal records and 84 per cent unquestionably normal records. On comparing the abnormal records for persons with and for persons without an epileptic subject in the family, we observed that definite abnormalities of cortical rhythm were six times as frequent in the group of relatives of patients as in the control group.

Influence of Age.—The distribution of the ages of patients when seizures began was as follows: under 5 years, 23 per cent; from 5 to 9 years, 31 per cent; from 10 to 19 years, 40 per cent, and 20 years and over, 6 per cent. The ages at onset and the present ages of the group are relatively low because parents do not ordinarily accompany adult patients to the hospital. The incidence of abnormal tracings among the relatives of patients in this small group was not affected by the age at which the patient's seizures began. The ages of the relatives ranged from 3 to 78.

Clinical experience with extramural patients has shown that puberty is a dangerous and old age a relatively safe period as regards the onset of seizures. If dysrhythmia is a constitutional defect, it should be present in all periods of life, unless altered by some environmental circumstance. Unfortunately, our group of relatives contained few below the age of 20 or above the age of 60. The distribution of ages of relatives and the percentage of definitely abnormal tracings in each age group are shown in the accompanying tabulation.

Age, Years	Number of Relatives	Relatives with Abnormal Tracings	
		Number	Per Cent
0-12	14	6	43
13-16	8	8	100
17-29	22	11	50
30-39	37	21	57
40-49	54	32	59
50 and over	49	25	51

This tabulation indicates that dysrhythmia in adults does not seem to be affected by the person's age. The fact that all relatives aged from 13 to 16, inclusive, had dysrhythmia suggests that any tendency toward cortical electrical instability is increased during adolescence. The relatively good showing of children under 13 years may perhaps be due to the fact that standards of normal for that age group are not yet crystallized.

Influence of Sex.—That sex is influential in the inheritance of epilepsy has not been generally recognized. The proportion of male

and female patients in any large group of patients may depend on extraneous conditions. Males constituted 48 per cent of Gowers' series of 3,000 patients [11] and 57 per cent of our series of 2,130 patients. Of the 94 patients in this series, 54 per cent were male and 46 per cent female. It is pertinent to inquire about the influence of sex on the occurrence of dysrhythmia. Of the 183 relatives examined, 80 (43 per cent) were male and 103 (57 per cent) female, a reflection of the custom that the mother accompanies the child to the hospital. Abnormal tracings occurred in 54 per cent of the male relatives and in 65 per cent of the female relatives; of the 55 pairs of parents the corresponding percentages were 55 and 69. With the relatives grouped with respect to the sex of the patient, 56 per cent of the relatives of male patients had dysrhythmia, against 64 per cent of the relatives of female patients. Only 50 per cent of the male relatives of male patients had dysrhythmia, against 66 per cent of the female relatives of female patients. The larger proportion of abnormal records for female relatives was expected because in the group of 2,130 patients female patients had 35 per cent more relatives with seizures than male patients had. Although the incidence of epilepsy among fathers and that among mothers were the same, epileptic daughters had 36 per cent more parents with epilepsy than epileptic sons had. Furthermore, a greater inheritance factor in females would explain the earlier onset of seizures in this sex. These are points which Gowers stressed forty years ago. Altogether the data suggest the possibility that females carry a greater inheritance factor as expressed by dysrhythmia and by family history than that carried by males. However, males suffer more injuries to the brain than females and, therefore, have as much or more clinical epilepsy. In other words, females have more "essential" and males more "symptomatic" epilepsy.

The electroencephalographic data do not suggest any sex linkage in dysrhythmia. When relatives were of the same sex as the patient, 58 per cent had dysrhythmia; when of the opposite sex, the percentage was 62.

Influence of Family History.—No patient gave a history of epilepsy in a grandparent, but 12 patients had an aunt, an uncle or a first cousin with a history of seizures. Such a history is only presumptive evidence that the related parent was the carrier of the abnormal gene. In 8 instances tracings were made of the parent who had a family history of epilepsy, and in all but 1 case dysrhythmia was present.

A history of syncope either in the patient or in a relative is usually disregarded, but a so-called fainting attack in reality might be a mild seizure, or a precursor of seizures. In the larger group of 2,130 patients, fainting among relatives of patients was encountered much

11. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases, London, J. & A. Churchill, 1901.

more frequently than in the control group. In the present series, 14 of the 143 parents examined had a history of fainting (5 fathers and 9 mothers). Of these, the electroencephalograms of 4 fathers and of 8 mothers were definitely abnormal; that is, 86 per cent of parents who had fainted had abnormal records, as contrasted with 60 per cent of all the parents. This small piece of evidence suggests, therefore, that a history of fainting should be viewed with suspicion.

Migraine has a statistical relation to epilepsy.[12] A history of migraine was present in 14 of the 143 parents (10 per cent), twice the incidence in a large control group; 13 were mothers and 1 was a father. Of these 14 parents 7 (50 per cent) had definitely abnormal records. This percentage is no greater than that of abnormality encountered in the parents without a history of migraine.

Psychic disturbances have been shown to be more frequent among the relatives of epileptic persons than in the general population. In this series there were only 2 parents who had a psychotic sibling. Both these parents had an abnormal electrical record.

Results in Parents.—There is an interesting contrast in the results when only one or when both parents were tested. When both parents were tested (110 parents of 55 patients), 62 per cent had definitely abnormal records. When only one parent was tested (33 parents of as many patients), only 48 per cent had abnormal tracings. This difference is hard to explain, except on the supposition that the more normal of the two parents brought the child to the physician and consented to be tested. Death or disappearance of a parent, or his disinclination to come to the hospital or to have electrical records made, may in some cases have been associated with abnormality of the electroencephalogram.

In 55 instances a record was obtained of both parents of the patient. Obviously, this information is of especial value in judging the frequency of heredity of dysrhythmia. The proportion showing various combinations of tracings is shown in the accompanying tabulation.

Normality of Tracing	Number	Per Cent
Both parents abnormal	19	35
One parent abnormal, one doubtful	5	9
One parent abnormal, one normal	25	46
One parent doubtful, one normal	3	5
Both parents normal	3	5

The surprising feature in this tabulation is the fact that definitely normal records for both parents were obtained in only 3 (5.4 per cent) of the families. In 2 of these 3 families the patient had jacksonian

12. Lennox, W. G.: Migraine and Epilepsy: Newer Concepts and Treatment, J. Med. **19**:284, 1938.

seizures, associated in 1 case with tumor of the brain and in the other with whooping cough. One or more parents had definite cortical dysrhythmia in 90 per cent of the cases. Other points will be discussed later.

Demonstration of Tracings.—Examples of the electroencephalograms obtained in the families tested follow.

Figure 1 shows samples of both abnormal and normal tracings obtained from members of the control group. The upper four records are abnormal. The first

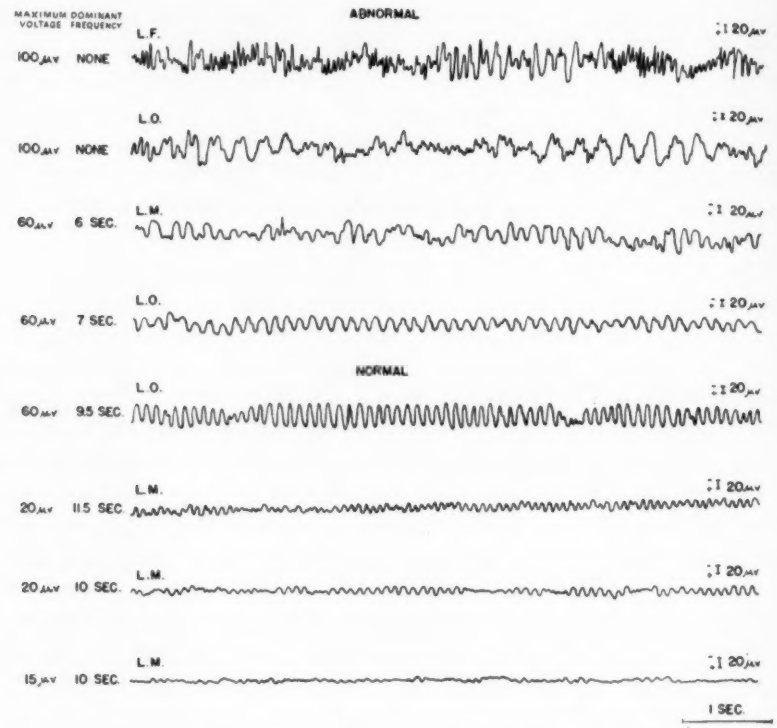

Fig. 1.—Examples of electroencephalographic tracings from members of the control group. The upper four tracings are samples of records considered definitely abnormal, and the lower four are samples of records considered normal. The column of figures at the extreme left gives the maximum voltage of the waves, expressed in millivolts. It will be noted that normal persons had a maximum voltage as high as 60 and as low as 15 millivolts in their dominant rhythm. The second column represents the dominant frequency of the waves, the two abnormal frequencies being, respectively, 6 and 7 per second, and the four normal ones from 9.5 to 11.5 per second. The letters at the left of each tracing are abbreviations for the region of the scalp to which the "active" electrode was applied, such as left motor (*L. M.*) and left occipital (*L. O.*). In all cases a ground lead was connected with both ears. At the right of each tracing is the signal made by 20 millivolts. The length of record corresponding to one second is shown in the lower right corner. The symbols are applicable also to subsequent figures.

two have no dominant frequency, fast waves alternating with slow. In the second record, fast waves of low voltage are superimposed on slow ones of high voltage (this subject had fainted twice at the sight of blood). The record of the third subject is abnormally slow, 6 per second, and occasional fast spikes are interspersed. Waves of the fourth tracing are uniform in voltage but are abnormally slow—7 per second. The voltage in this tracing is no greater than in the first of the normal tracings. The four normal tracings show voltages which vary between 15 and 60 millivolts. However, they are all normal in rate, between 9.5 and 11.5 per second.

The tracings in figure 2 were chosen to illustrate the types of abnormal waves encountered in "normal" parents. The presence of fast, spiky waves alternating

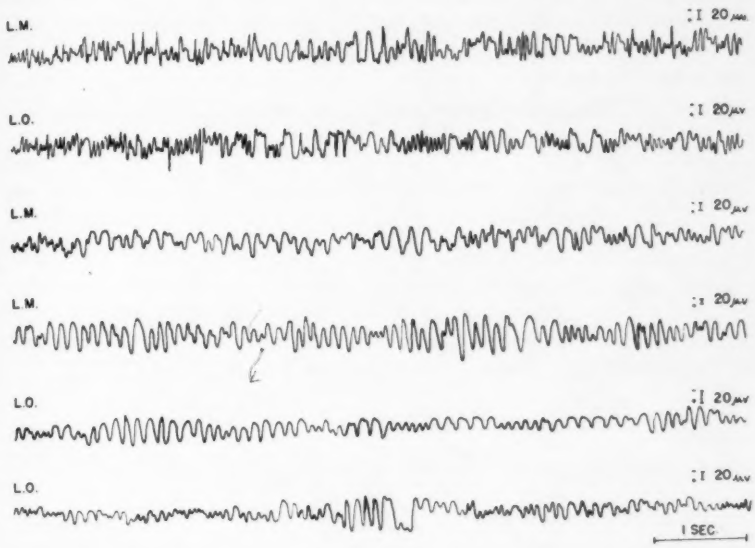

Fig. 2.—Tracings illustrating dysrhythmias encountered in 6 normal parents of patients with epilepsy. Each of the six tracings is a small section from one of the leads of a parent who showed dysrhythmia. The abnormalities are of various types: first, the predominantly slow rhythm, as in the fourth tracing; second, sudden changes from fast to slow activity, as in the second, and third, a combination of fast and slow waves, as in the first. Other combinations of abnormalities will be observed in subsequent figures.

with abnormally slow waves is especially prominent in the first and second tracings. The remaining four tracings all display waves which are abnormally slow and of increased voltage.

Records made for both parents show various combinations of results. One parent may have pronounced dysrhythmia, while the spouse may have a normal rhythm or varying degrees of abnormality. Figure 3 shows the tracings of 3 pairs of parents. In each instance the record of one parent is normal and that of the spouse is definitely abnormal.

Because the 3 a second alternate wave and spike formation is diagnostic of petit mal, its appearance awakens peculiar interest. Figure 4 represents a family

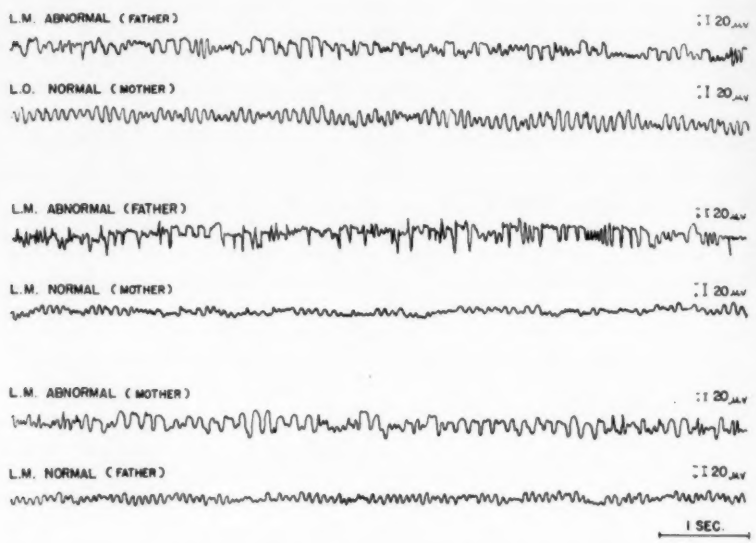

Fig. 3.—Tracings from 3 pairs of parents, with dysrhythmia present in only one of the parents. In each pair the upper tracing is definitely abnormal and the lower normal. The voltages are not directly comparable. Reference to the calibration of voltage at the right shows that the waves of the abnormal parent would have been much higher if the amplification had been the same for both parents.

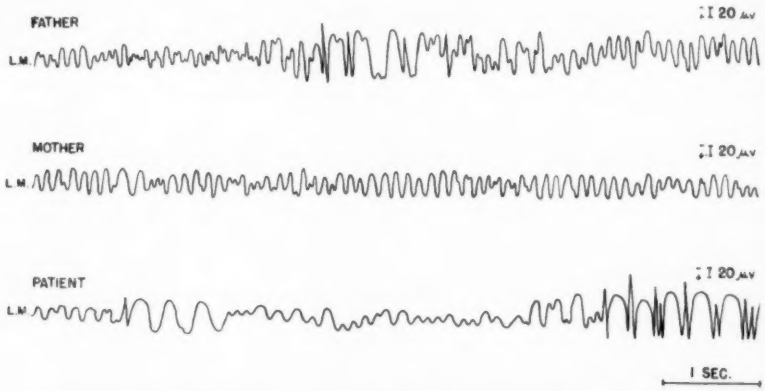

Fig. 4.—Tracings from 3 members of one family. In the lower tracing, that of the patient, the spike and three waves near the left end indicate a subclinical seizure, and a series of alternate 3 a second waves and spikes at the right marks the beginning of a clinical attack of petit mal. The second tracing, that of the mother, shows moderate abnormalities in slowness of waves. The upper tracing, that of the father, taken after overventilation, shows the characteristic alternate wave and spike formation of petit mal. Except for the patient, none of the family had a history of any neuropsychiatric disorder. All 3 members of the family were exceptionally intelligent and apparently well balanced.

in which a patient had clinical and a parent subclinical petit mal. The patient, whose record is on the lower line, had a history of frequent attacks of petit mal and occasional attacks of grand mal. At the left of his tracing is a record of subclinical petit mal, consisting only of a spike and three waves, and at the right the beginning of a record of clinically recognizable petit mal. The mother's record was classed as questionable, having occasional slow waves. The father's record showed, during overventilation, the typical 3 a second wave and spike formation of petit mal, which persisted for two seconds. Neither the mother nor the father, an intelligent man filling an important administrative position, gave any personal or family history of seizures, migraine or mental disorder.

Particularly valuable are records of a whole family group. Figure 5 comprises tracings from the 6 members of one family. The patient came to the hospital because of two convulsions which she had experienced in recent months. Her

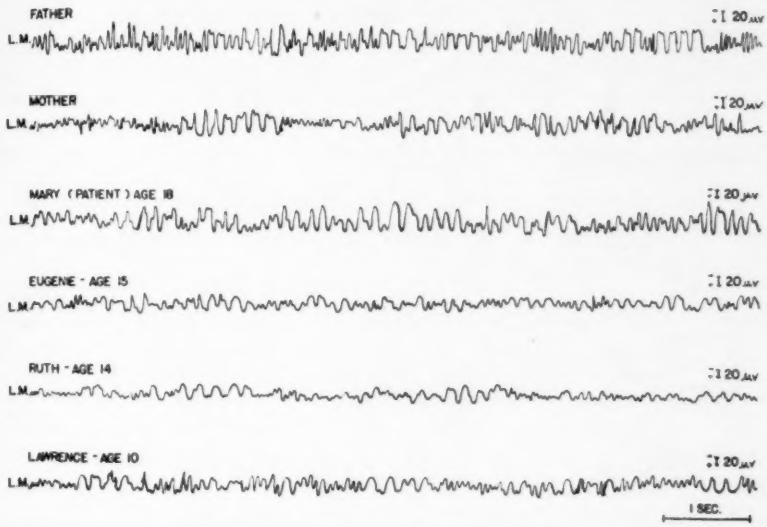

Fig. 5.—Tracings from a family of 6, 2 of whom had a history of seizures. The third tracing is that of the patient, Mary, who had had two convulsions. The mother had had probable seizures in childhood, and the 2 younger sisters of the patients had a history of syncope. All the records are abnormal, particularly that of the father, whose personal and family histories were not significant.

record, line 3, shows preponderance of abnormally large, slow waves. The mother gave a history of fainting frequently during the period of adolescence. Close questioning disclosed that these were probably mild psychomotor attacks. Her record also showed many large, slow waves. The father had no significant personal or family history, but his record was fully as abnormal as the mother's. There were 3 children, all of whose histories were normal, except that the 2 adolescent sisters of the patient had experienced several fainting attacks, which on questioning seemed to be purely syncopal. The records of all 3 sisters were abnormally slow.

Another family of 6, all intelligent and well educated, presented an enlightening constellation of facts (fig. 6). The family histories of the husband and wife were

devoid of seizures. The husband (who was not a blood relative of the patient and was, of course, not counted among the relatives) had had a few typical attacks of ophthalmic migraine. His electrical record was abnormal. The patient, now aged 54, had toxemia of pregnancy and thrombosis of the vessels of the legs, lungs and eye during her first pregnancy, at the age of 28. Between the ages of 35 and 45 she experienced "waves of dizziness," which her physician called petit mal. In an effort to relieve this condition artificial menopause was brought about, but the attacks changed to grand mal. For the past nine years these have come every three to five weeks, are nocturnal and are usually preceded by one or more short psychic seizures in which the patient puckers her mouth and says "yes, yes." Attacks are followed by several days of elevated temperature. The use of dilantin sodium controlled the convulsions, but at intervals of about a month she has several

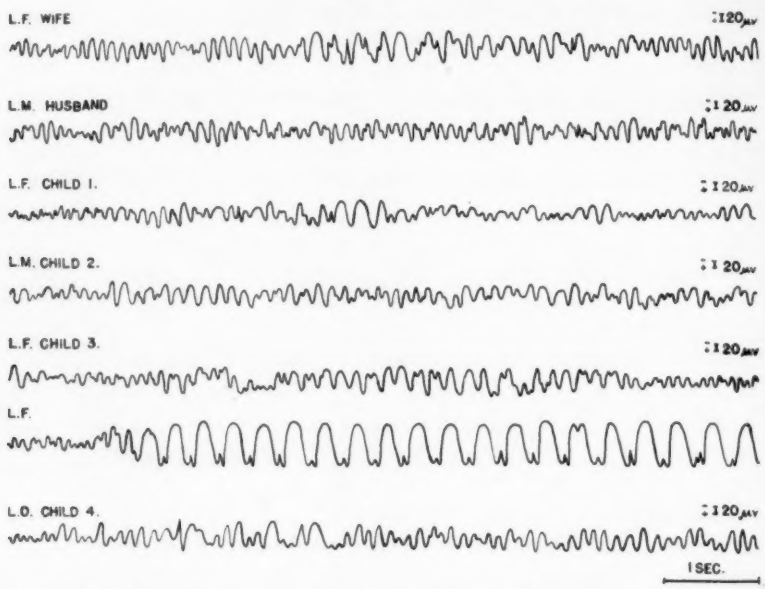

Fig. 6.—Tracings from a family of 6, 1 of whom, the wife, had had seizures, with a history suggesting symptomatic onset. The husband had had attacks of migraine. None of the children had significant histories, but all had abnormal records, particularly the third. The upper of the two tracings for this child was taken during a normal period; the lower, which shows the typical 3 a second wave and spike formation of petit mal, occurred after overventilation. On a subsequent occasion asymptomatic petit mal occurred spontaneously.

days during which she feels dazed and has an elevated temperature. Her electroencephalographic record was abnormal and of the psychomotor type, with, however, an occasional alternate wave and spike pattern suggestive of petit mal. The oldest child, aged 26, had had a recent injury of the head, with a short period of unconsciousness. The youngest child, aged 14, had been something of a "problem child." The electrical records of all 4 children were definitely abnormal. The tracing for the youngest child had an occasional isolated wave and spike formation from over the frontal region. The third child had definite electrical signs of petit mal (without clinical symptoms) on two occasions.

Similar Twins.—In the study of inheritance twins have a peculiar value. We have spoken of the electrical evidence from twins who are normal or have various neurologic conditions. We shall now record briefly the observations on similar twins, one or both of whom had seizures or were the relatives of an epileptic person. There were 5 pairs of these twins. Two were not included in this series of 94 cases.

In the first pair of twins, one had poorly described periods of unconsciousness, presumed to be of epileptic origin. Later hysterical paralysis developed. Both his and his brother's electrical records were found to be normal. The question arises whether the original diagnosis of epilepsy was correct in this case. In the second pair, each twin had epileptic seizures.

In 1 of the 3 other families, neither twin had seizures, and in each of the remaining 2 families only one twin had seizures. The tracings of the first of these 3 families appear in figure 7. The record of the mother was normal. The father and 10 year old, healthy similar twin sisters had abnormally slow square-topped waves, most prominent in the motor leads. The patient, a boy of 14, had a 3 a second, wave and spike record of petit mal. The only suggestive fact in the personal or family history is that an aunt of the father was in a hospital for mental disease.

In each of the other 2 families only one twin had epilepsy, the result apparently of intrauterine or birth injury, but in both families the "normal" twin had dysrhythmia. One of these cases is a perfect one for demonstrating the factor of inheritance in so-called symptomatic epilepsy (fig. 8). The patient was the second born of similar twins. Both births were apparently normal. The patient, however, presented palsy of the right side a few days after birth, which cleared up after a few months. Convulsions began on the right side and have come in series at intervals ever since. He also had frequent attacks of petit mal. The children could not be told apart in their early years, but at present the patient is obese and at the same time taller than the normal brother. He is mentally deficient and of unruly disposition. The patient's electrical record shows a preponderance of large, slow waves during the interval between attacks and the typical 3 a second, wave and spike formation during the attacks of petit mal. The record of the normal brother, who is unusually alert and intelligent, also contains large, slow waves of the same type, though of lesser voltages, as those of his epileptic twin, but it shows no wave and spike formation. The record of the sister is normal. The records of both parents are definitely abnormal. Aside from the occurrence of epilepsy in the patient, there is no personal or family history of this disorder, except that the father's brother, after an accident, became an inmate of a hospital for mental disease.

Two of the 5 sets of twins had no history which would suggest that there had been any injury of the brain. In 1 of these pairs there were only the presumably hysterical episodes in one of the twin brothers, and in the other there were no seizures in either of the twin sisters (fig. 7). The electroencephalographic records of the twins in these 2 sets were indistinguishable. In the other 3 pairs of twins, in which one or both had had a long series of convulsions, the tracing of the twin with the convulsions, or with the most convulsions, was the more abnormal. Presumably, pathologic changes in the cerebrum, which were either the cause or the result of convulsions, increased the dysrhythmia which was already present.

Although, as previously mentioned, epileptic seizures occurred in both similar twins in only about 70 per cent of cases, in the present series either a normal or an abnormal rhythm was present in both twins in every set examined.

Transmission of Types of Dysrhythmia.—Presentation of twin material is an appropriate occasion for discussing whether a certain type, or only some sort, of irregularity is transmitted. We believe that epilepsy is characterized by a disturbance in the rate-regulating mechanism of the brain and the electroencephalogram by an instability of rate, rather than the presence of a rate which is consistently either fast or slow. The

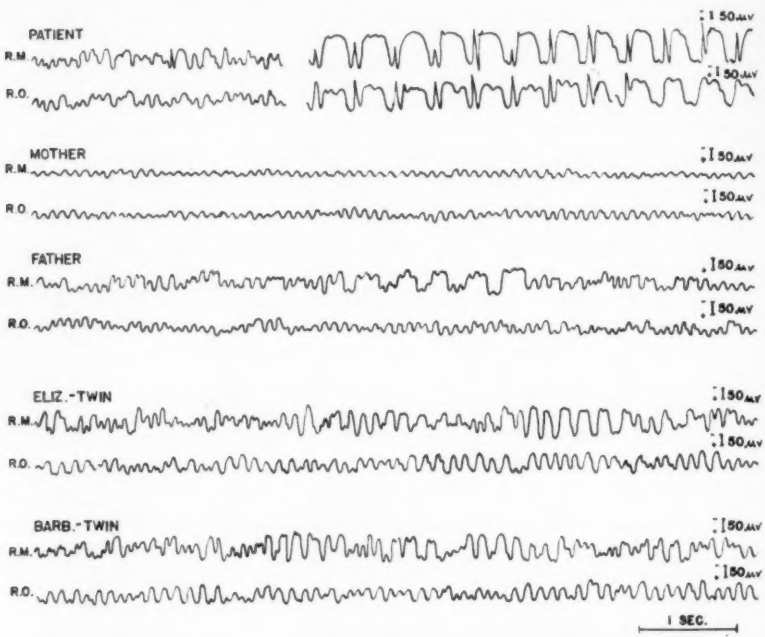

Fig. 7.—Portions of the electroencephalographic records of a patient with petit mal and (from top to bottom) those of his mother, father and younger identical twin sisters (Gibbs, Lennox and Gibbs [4]). Only leads from the right motor and occipital regions are shown. In the patient's record the right hand portion was made during an attack of petit mal, the left hand portion during a subclinical seizure. The mother's record is wholly normal. The father and 2 daughters have abnormally slow waves, predominantly in the motor area.

majority of patients have more than one type of seizures, and their electroencephalograms may show different types of abnormality on different occasions. Therefore, we should not expect a tracing of a relative of a patient made on a single occasion to show the same type of abnormality as a tracing of the patient himself. The crucial evidence on this point is that derived from identical twins. As stated in the previous section and as illustrated by the figures of those families which contained similar

twins, the tracings of the twins show not simply a dysrhythmia but the same type of dysrhythmia. In both of the uninjured nonepileptic twins, illustrated in figure 7, the dysrhythmia was localized in the motor areas. In 2 pairs of twins only one member of which had received an injury of the brain and had become epileptic, the fundamental dysrhythmia of both the epileptic and the nonepileptic twin were similar. None of the uninjured twins in our series had petit mal. Critchley and Williams [13] examined a pair of uninjured identical twin sisters, only one of whom had clinical petit mal. However, the supposedly well sister had bursts of alternate wave and spike waves in the electroencephalogram which were similar to those of the epileptic sister. Observations on similar twins need to be greatly extended, but the evidence so far gathered indicates the genetic importance of a particular type of dysrhythmia.

When we approach the subject of the similarity of electroencephalograms in other relatives, the evidence is blurred by the factor of mixed heredity. A note was made of the most prominent abnormality in rate in the tracings of relatives. The following tabulation shows the proportion of each type.

Cortical Frequency	Relatives, per Cent
Abnormally slow	34
Slow and fast	56
Abnormally fast	2
Wave and spike	8

The most striking difference between patients and relatives is the fact that 50 per cent of the former and only 8 per cent of the latter had electroencephalographic evidence of petit mal. Approximately two thirds of the patients with the wave and spike pattern had this as the outstanding abnormality, and one-third had abnormally slow waves as well. That a greater proportion of patients than of relatives had electroencephalographic evidence of petit mal is perhaps accounted for by the fact that petit mal, for reasons as yet unknown, is predominantly a symptom of childhood and youth, attacks tending to become less frequent or to disappear as the patient becomes adult. Long runs of wave and spike activity, such as occur in clinically evident petit mal in childhood, are in our experience exceedingly rare in adults. If this were the only explanation of this discrepancy one would expect that younger relatives would show more of this type of dysrhythmia than older relatives. This was not necessarily true in our group, but a series with a large number of children is needed. Another possible explanation of the greater frequency of petit mal in patients than in relatives would be that the attacks of petit mal are associated in some way with clinical expression of the

13. Critchley, D., and Williams, D.: Personal communication to the authors.

underlying dysrhythmia. A case in point is presented by the similar twins (fig. 8) of whom both showed fundamental slowness of rhythms, but only the epileptic twins with cerebral injury had petit mal. On the other hand, of the 8 relatives who had isolated or serial waves and spikes, only 2 had a history of petit mal. In all 8 cases, the patient to whom they were related had petit mal.

The histories of 3 of the families are particularly suggestive. In 1 family the child had pure petit mal as evidenced, both clinically and electrically. Her mother had had petit mal without grand mal in childhood, which disappeared during adolescence, an example of so-called pyknolepsy. The father's record was normal, so that presumably the

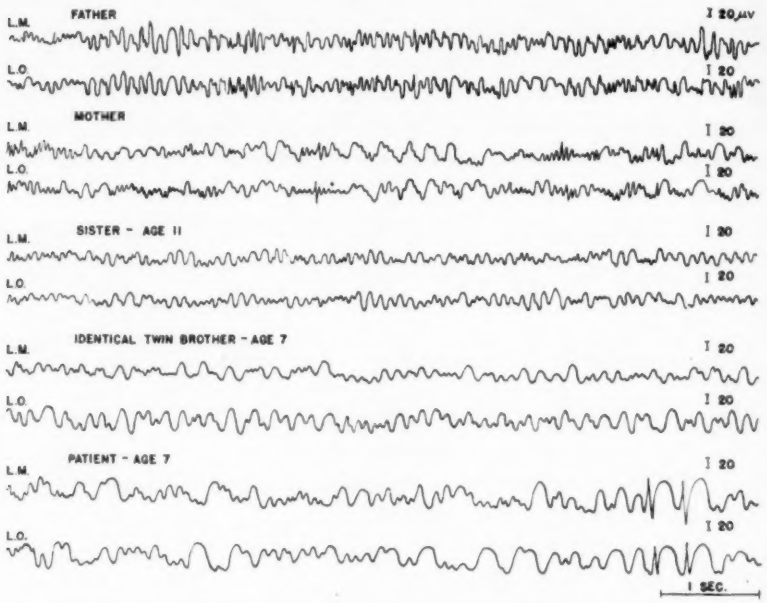

Fig. 8.—Tracings from a family of 5 in which seizures occurred in one of similar twins. The only normal tracing is that of the youngest child. There was no family history of seizures. The tracing of the epileptic twin contains many patterns typical of petit mal but otherwise resembles that of the normal twin.

mother carried the full inheritance. A brother's record was normal. In the second family (fig. 6) the mother had a clear history of petit mal, though only isolated waves and spikes appeared on the record. Three of the 4 supposedly normal children had as much or more petit mal activity. In the third family the normal father had electrical evidence of petit mal (fig. 4); the normal mother had slow waves, and the patient, a son, had waves and seizures typical of both grand and petit mal.

This aspect of the problem should be greatly clarified by the collection and study of electrically analyzed records.

Evidence of Other Investigators.—These observations are of far reaching importance with reference to the problem of inheritance in epilepsy and related conditions. Evidence gathered by other workers is desirable. Two contributions have appeared since our preliminary reports. Löwenbach [14] examined 37 relatives, including cousins, uncles and aunts, of 11 epileptic children. Of these, 17, or 46 per cent, had abnormal electroencephalographic records. The report deals principally with 1 family unit, of which 15 members were examined. Ten of these (66 per cent) had abnormal records. Strauss, Rahm and Barrera [15] examined 93 parents or siblings of 31 epileptic patients. Of the 93, 27 per cent had definitely abnormal records and 15 per cent had suggestive records, a total of 42 per cent with evidence of epilepsy. Both parents were examined in 8 families; tracings of both parents were normal in 4 instances. Omitting the 5 families in which records were only suggestive, the authors found that the patients could be divided into two groups. In the first group, comprising 54 per cent of the total, 1 or more of the relatives examined had dysrhythmia. In the second group, comprising 46 per cent of the total, none of the relatives had dysrhythmia. The authors therefore concluded that there are two forms of epilepsy, one with and the other without abnormal electroencephalograms among the relatives. This conclusion seems unwarranted because of unequal sampling in the two groups. In the first group (the one with familial dysrhythmia) the number of relatives examined per patient was 42 per cent greater than in the second, or "negative," group. One relative only was examined in 7 per cent of the "positive" families and in 41 per cent of the "negative" families. The sharpest disagreement between their results and ours is for those families in which records were taken of both parents. Of our 55 families the records of both parents were entirely normal in only 5 per cent, whereas of their 8 families the records of both parents were normal in 50 per cent.

The percentage results of neither of these two contributors can be compared with ours because of differences in the criteria used. Löwenbach counted as abnormal "all wave-and-spike groups regardless of frequency, and all slow waves of a frequency of 3 to 4 per sec. provided they appeared spontaneously, or in long runs and for a considerable time after the end of an overventilation period, and provided their amplitude reached or exceeded 200 microvolts." Strauss, Rahm and Barrera counted as abnormal series of waves with a rate of 3 to 6 per second and a voltage of 50 microvolts, including abnormally slow waves which

14. Löwenbach, H.: Electro-Encephalogram in Healthy Relatives of Epileptics: Constitutional Elements in "Idiopathic Epilepsy," Bull. Johns Hopkins Hosp. **65:** 125, 1939.

15. Strauss, H.; Rahm, W. E., and Barrera, S. E.: Electro-Encephalographic Studies in Relatives of Epileptics, Proc. Soc. Exper. Biol. & Med. **42:**207, 1939.

occurred in adults after overventilation. Neither of these workers mentioned control records obtained from persons of nonepileptic families or the length of time of the recording. Apparently no attention was paid to series of abnormally fast waves or to the voltage of abnormal waves in relation to the voltage of the normal portion of the subject's record. Apparently no allowance was made for age. In our experience a dominant frequency of less than 8 per second is abnormal for the adult, whereas a dominant frequency of 7 per second is normal for a 5 year old child. Finally, the authors included slow waves which occurred in adults after ventilation, a practice which is open to the criticism that overventilation, if vigorous enough, uniformly produces great slowing of brain waves.

These articles indicate the need for uniformity of criteria of what is abnormal based on records from control subjects. The ability to state more exact specifications will come, we believe, with the use of electrically analyzed records. However, the evidence (published and unpublished) of these and other workers supports the main thesis that a substantial proportion of the near relatives of persons subject to seizures have cortical dysrhythmia.

COMMENT

The significance of the dysrhythmia of relatives of epileptic persons requires discussion.

Constancy of Dysrhythmia.—How constant is dysrhythmia in a person who has no significant symptoms? The pattern of normal brain waves traced on a record is the shadow of the constantly changing activity of the cortex of a living brain. Therefore, it is modifiable by activity of the brain or by a variety of physiologic factors. Our studies indicate that the abnormal rhythms found in patients with epilepsy vary a great deal from time to time. On one day the record may be abnormally fast and on another day abnormally slow; on another day there may be no demonstrable abnormality. The area of maximum abnormality may shift from one part of the cortex to another. Records of patients are modifiable by artificial means, though certain patterns (notably that of petit mal) are much more easily influenced than others. As has been stated, the abnormal records of normal relatives contain few wave and spike formations. Whether the abnormal rhythms of relatives are more constant and less easily altered by drugs or by changes in the body chemistry than the abnormal rhythms of patients has yet to be determined. We suspect that they are. Records of several of the relatives with abnormal waves repeated at intervals of weeks or months were found to have changed little. This fact, together with the rather continuous disorder apparent in the records of relatives, suggests that in them the dysrhythmia is not so definitely paroxysmal as in the epileptic subjects.

The percentage of abnormal records was 26 per cent higher among siblings than among parents in Strauss's series. In ours, the percentages were nearly the same. Whether siblings and younger persons have more dysrhythmia than parents or older persons is a matter which requires wider observations. In our group the incidence of dysrhythmia in relatives over 50 years of age was low (47 per cent). A dysrhythmia which tends to "die out" would help to explain the tendency of the occurrence of seizures in epileptic subjects to decrease with advancing age and the relative rarity with which seizures begin in adults.

Possibly Acquired Dysrhythmia.—Could the abnormal waves of parents be due to acquired causes? Dysrhythmia may follow injuries or organic degenerative diseases which involve the cortex. A patient with adenoma of the islets of the pancreas with recurring periods of coma had dysrhythmia, which disappeared a year after successful pancreatomy. Only 2 of the relatives with dysrhythmia had a history of serious injury to the head which antedated the examination. None had mental impairment or evidence of degenerative disease of the brain. Dysrhythmia due to trauma would be more localized than the dysrhythmia present in the relatives in this series. In many instances abnormality was more pronounced in a certain area (usually the motor or occipital), but in no instance was the abnormality as sharply localized as in cases of tumor or trauma involving the cortex.

Specificity of Symptoms of Dysrhythmia.—Are the observed abnormalities specific for epilepsy? Our answer to this important question is "No." On looking backward from the epileptic child to the parent with dysrhythmia, one must believe that the abnormal waves of the parent spelled potential epilepsy. But on looking forward from the siblings of the patient who exhibit dysrhythmia one does not know whether or not children of theirs which show clinical signs will have epilepsy, personality or behavior disturbances, migraine or psychosis. Dysrhythmia is present in an unusual proportion of problem children,[16] in certain persons having periodic alterations in personality or in mental acuteness (attacks which are not ordinarily classed as epileptic but are probably mild psychomotor seizures) and, finally, in persons with schizophrenia and other abnormal mental states.[17] Just as a person with heart disease may exhibit a variety of symptoms (or no symptoms at all), a

16. Jasper, H. H., and Nichols, I. C.: Electrical Signs of Cortical Function in Epilepsy and Allied Disorders, Am. J. Psychiat. **94**:835, 1938.

17. Berger, H.: Ueber das Elektrenkephalogramm des Menschen, Arch. f. Psychiat. **106**:577, 1937. Hoagland, H.; Cameron, E., and Rubins, M. A.: The Electro-Encephalogram of Schizophrenics During Insulin Treatments: "Delta Index" as Clinical Measure, Am. J. Psychiat. **94**:183, 1937. Davis, P. A., and Davis, H.: The Electroencephalograms of Psychotic Patients, ibid. **95**:1007, 1939. Gibbs, Gibbs and Lennox.[7]

person with dysrhythmia may have a convulsion or lapse of consciousness, commit a crime or be entirely normal. The probabilities are that all of the relatives in this group who have disordered brain waves but are now normal will remain so. The group already contains nearly as many epileptic persons as it is entitled to, although if one of the adults with dysrhythmia should suffer cerebral trauma, tumor of the brain or cerebral thrombosis he might even yet have seizures.

The question naturally arises whether "normal" relatives with abnormal brain waves manifest any unusual or unfortunate characteristics. Many of them do. Those who were described as "uncooperative," "unreasonable" or "flighty" or who had a history of alcoholism or unsocial conduct often had abnormal records. On the other hand, some of the most abnormal records were obtained from relatives who seemed unusually intelligent and well balanced. Many of the dysrhythmic persons were college graduates; 4 of the 37 fathers with dysrhythmia were successful physicians. In 1 family an alcoholic "problem father" had a beautifully normal record, whereas that of the mother, who was the "mainstay" of the family was abnormal. The persons with dysrhythmia in the control group all had superior intelligence, were successful and appeared to be well adjusted. Obviously, dysrhythmic but nonepileptic persons require careful study from many points of view.

Degree of Abnormality and of Inheritance.—An important question arises next: Is the degree of abnormality of the electroencephalographic record any measure of the degree of inheritance? The answer to this question depends in part on whether inheritance is a variable quantity or whether, as some assume, it either is not present at all or is present to a fixed and maximum degree. The electroencephalographic tracings vary all the way from perfectly normal to extremely abnormal. We suspect that parents with extremely abnormal records will have more children with dysrhythmia than parents whose records approach the normal, but demonstration of this point will require a larger series of full families with electrically analyzed records which will permit of classification of various degrees of abnormality. The problem is especially complicated when both the father and the mother have abnormal records. It is possible that children would fare better if one parent had an extremely abnormal and the other a normal record than if both had only mildly abnormal records.

Relatives of "Symptomatic" Epileptic Persons.—For centuries writers have made a sharp distinction between "essential" and "symptomatic" epilepsy. Although the definition of each has often been blurred, most authors have regarded "essential" as synonymous with "hereditary." We have expressed the belief that a sharp separation of these two groups is unjustified because tabulation of our statistical data

has shown that the "symptomatic" group of epileptic patients (those whose seizures had begun subsequent to an injury of the brain) had three times as many near relatives with seizures as had persons in the general population (the "essential" group has five times as many). However, we found that if the injury or tumor of the brain (and subsequent epilepsy) did not occur until the patient was adult, this group did not have more relatives with epilepsy than any group in the general population.

In securing tracings of relatives, no effort was made to confine observations to patients with "essential" or "symptomatic" epilepsy. Of the 94 patients, 15 (17 per cent) would ordinarily be classed as having "symptomatic" epilepsy; seizures from the beginning were jacksonian in type, or there was a history of injury at birth or of other injury to the brain, infection or tumor which preceded the onset of seizures. One of these family groups is shown in figure 8. The only case of proved tumor of the brain was that of a 10 year old boy. The records of both parents were normal. Of the 27 parents and siblings of the patients with "symptomatic" epilepsy, 60 per cent had abnormal electrical records, an incidence which is the same as that of dysrhythmia in the group with "essential" epilepsy. Of course, a larger group with symptomatic epilepsy is needed, with attention to the age of the patient, since if seizures began early in life the hereditary factor is of greater importance.

If "essential" is synonymous with "hereditary" and if dysrhythmia is present in the parents of most of the patients with so-called symptomatic epilepsy, the question arises whether there is such a thing as "symptomatic" epilepsy. Of our group of 100 control subjects, approximately 10 per cent had definite dysrhythmia and another 6 per cent had "borderline" records. Therefore, in cases of any physical disorder in which the incidence of seizures is less than 10 or 20 per cent the presumption is that some dysrhythmia was already present and that the pathologic changes in the brain or the physical disorder increased it to the point of clinical externalization. After traumatic injury to the brain, less than 20 per cent of the injured persons later had seizures, and possibly all of them had antecedent dysrhythmia. On the other hand, among persons with tumor involving the frontal or parietal lobe, the incidence of seizures may be as great as 50 or 60 per cent. In this group one must conclude either that the majority of epileptic patients with tumors had no antecedent dysrhythmia, and their seizures were therefore wholly the result of the injury caused by the tumor (symptomatic epilepsy), or else that they had dysrhythmia (or predisposition) too slight to appear abnormal in the unanalyzed tracing. There is, of course, the possibility that cerebral tumors and dysrhythmia are developmentally linked, or, expressed differently, that the predisposition to cellular proliferation

and to cellular discharge have a common chemical basis, at least in those areas of the brain in which the electrochemical organization of the brain is most influential or most easily disturbed.

More light will be thrown on this question by the accumulation of tracings of the relatives of adult patients with tumors of the brain and subsequent seizures. Even in the case of injection of a convulsant agent like metrazol, the "susceptibility" to convulsions varies with species of animals and with individual persons. Persons subject to seizures have convulsions with much smaller doses of metrazol than do normal persons. It will be important to know whether a nonepileptic person requires a smaller dose of metrazol for production of a convulsion if he has dysrhythmia than if he has normal waves, and if so, whether the degree or type of abnormality is influential. There seems to be a parallelism between the greater ease with which convulsions are induced in rabbits as compared with cats and the greater irregularity in the electroencephalogram of the rabbit.

Treatment of Dysrhythmia.—Can the dysrhythmia of a person who is without clinical symptoms of epilepsy be treated with the hope of thereby preventing him from subsequently having seizures or other undesirable symptoms? Presumably, parents with dysrhythmia are beyond the age when seizures are likely to develop. However, treatment of a person with dysrhythmia, especially a child, would seem to be worth a trial. At present, hope is centered in dilantin sodium, but we have observed that improvement of the electrical record by no means parallels any clinical improvement which may follow the use of this drug. Whether the clinical or electrical record is the best indication of the patient's ultimate state has yet to be determined. Occasionally, drug treatment will apparently do away with a disordered rhythm. Such a case is that illustrated in figure 9. A girl aged 18 had been having psychomotor seizures for several years at about weekly intervals. Phenobarbital had little influence. Dilantin sodium caused cessation of attacks and great improvement in disposition and ability to learn. A tracing taken after a year of freedom from attacks showed a nearly normal record (line 2), which was in sharp contrast to the record taken before medication. Her record after treatment was much better than that of the other 3 "normal" members of the family. She had no evidence of injury to the brain and since her parents and brother all had dysrhythmia, the abnormality of her record was undoubtedly of genetic origin. Whether the dysrhythmia of the other members of the family could be improved also is an important question not yet answered.

Cortical dysrhythmia, although a transmissible constitutional characteristic, is not laid down, like a finger print, in fixed tissues, but is functional and physiologic, an ever shifting shadow of a disturbance

of the fundamental electrochemical activity of the brain. This hereditary trait is therefore potentially influenceable by physiologic and chemical changes in the brain. The wave and spike pattern of petit mal can be abolished temporarily by the inhalation of carbon dioxide. Possibly a chemical means can be found for doing away with all dysrhythmia.

If the abnormal electrochemical activity of the brain could be corrected by chemical means, might chemistry also alter the genes which are responsible for this abnormality and thus make possible quick elimination of dysrhythmia from the race? Although this suggestion seems fantastic, presumably genes themselves are large chemical molecules; they have, in fact, been altered by exposure to roentgen rays.

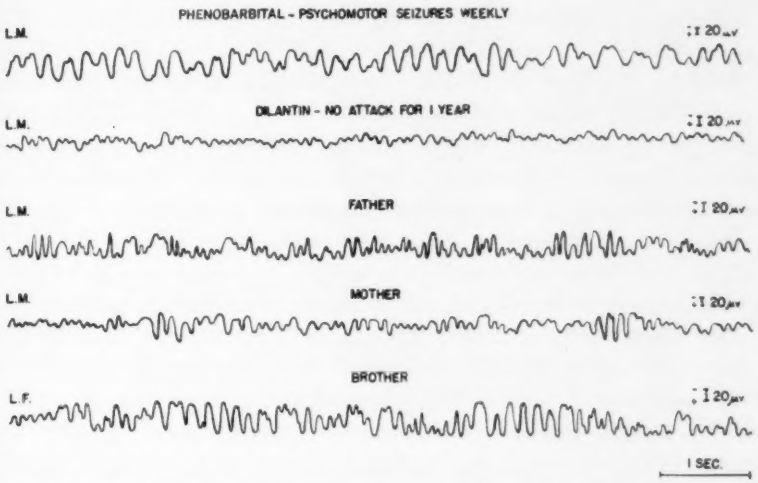

Fig. 9.—The effect of dilantin sodium on cerebral dysrhythmia. The upper tracing is that of a patient with a history of psychomotor attacks occurring weekly while taking phenobarbital, which was ineffective in controlling the attacks. The dominant frequency of the waves in her record is 4 or 5 per second. The second tracing, which is essentially normal, was taken a year later. During the year she had been taking dilantin sodium and had had no seizure. At the bottom are the tracings of the 3 other members of her immediate family, none of whom have symptoms, although the father has a domineering, irascible temper. The tracings of all 3 are abnormal.

Bearing on Eugenics.—This evidence brings forward some practical points in regard to eugenics and epilepsy. These points are so far reaching in their significance that the observations which we are reporting here should be extensively and painstakingly reviewed by others. Cerebral dysrhythmia obviously is an inheritable trait. Most students believe that epilepsy is a recessive mendelian trait, skipping generations at a time. But the antecedent dysrhythmia would seem to be a dominant trait, appearing in members of each generation according to well defined

laws. But where does dysrhythmia as a clinically silent trait end and dysrhythmia as a precursor of observable symptoms begin? Lightning is not thunder, and dysrhythmia is not clinical epilepsy, but the two are inextricably mixed. The borderline between dysrhythmia with and dysrhythmia without symptoms is a hairline. In some patients only a minimum of impairment of intellectual functions can be detected during an attack of petit mal which writes a turbulent record on the electroencephalogram. In a case of psychic epilepsy a cross word may be the only outward expression of a series of slow waves of high voltage.

However, leaving the puzzles of the borderland between disordered cortical rhythm and seizures, one has the problem of eugenics associated with normal "carriers" of a dysrhythmia which is, or represents, a predisposition to seizures. (We do not use "carrier" in the narrow technical sense of a person who transmits a disorder but cannot himself have the disorder.) If the dysrhythmia is, or reflects, the predisposition, then electroencephalography fulfils a dream of the ages. It provides a means of determining healthy carriers of epilepsy and allied disorders and gives society a chance to eliminate this trait by means of eugenics. Many years ago Davenport and Weeks [18] proposed that simple segregation of all epileptic persons would rid the world of this trouble in a single generation. Instead, it would have required an endless length of time because healthy "carriers" are as potent in transmission as those who are affected. They outnumber the affected ones many times, and they could not be identified. Whether society can and will use the electroencephalogram as a tool for betterment of the race carries one into the realms of sociology, religion and politics. Presumably, as with other aspects of genetics, the more intelligent, conscientious and economically productive members of society would limit their offspring, while the dependent and irresponsible members would merrily continue with procreation.

In order to maintain a proper perspective on this problem, certain points deserve emphasis. First, it must be remembered that epilepsy does not stand alone as a hereditary ailment, but has the company of many other common medical disorders, such as diabetes, cancer and cardiovascular diseases. Epilepsy and diabetes are closely similar with respect to their incidence among relatives and similar twins. Even infections cannot be eliminated from the list of diseases in which heredity plays a prominent part. Webster [19] has shown that susceptibility to infections is an inheritable trait in mice. Tuberculosis is as common as epilepsy in similar twins. Furthermore, greater absolute results would

18. Davenport, C. B., and Weeks, D. F.: A First Study of Inheritance of Epilepsy, J. Nerv. & Ment. Dis. **38**:641, 1911.

19. Webster, L. T.: Heredity in Infectious Disease, J. Heredity **30**:365, 1939.

attend the celibacy of persons with migraine than of those with epilepsy, for patients with migraine have half as many epileptic relatives as do epileptic patients, and migraine is ten times as prevalent.[11]

Disregarding the factor of betterment of the race and thinking only of the individual, we remind relatives of epileptic persons that the lightning of epilepsy rarely strikes in the same family twice. Only 1 of 40 of a patient's near relatives have seizures, so that presumably the average patient could have 40 descendants, and only 1 of them have epilepsy. (Of course, much would depend on the person he marries, a question to be discussed shortly.)

Searchers after new knowledge sometimes realize the force of the adage: "Where ignorance is bliss . . ." Knowledge of which parent transmitted the epilepsy and which of the brothers or sisters of the patient are also predisposed may be a burden which the physician hesitates to place on the already burdened minds of the patient's relatives. Yet true information can be the only basis for intelligent planning of the prophylaxis and the treatment of epilepsy.

Numerical Applications of Data.—How many normal "carriers" of epilepsy are there? As stated before, approximately 2.4 per cent of the near relatives of noninstitutional patients have a history of seizures. Of the 183 near relatives of the patients in our series who were examined electrically, approximately 60 per cent had dysrhythmia. Therefore, persons with dysrhythmia (carriers of a trait which may manifest itself in seizures or allied disorders) outnumbered persons with seizures about 25:1. Since approximately 0.5 per cent of the population has epilepsy, we may conclude that approximately 12 per cent of the population has a predisposition to epilepsy or an allied disorder—about 15,000,000 in the United States. Ten per cent of those in our control group had pronounced dysrhythmia, which is in line with the foregoing estimate, though a larger group of persons taken at random will need to be examined. The number as finally determined might be 5 or 15 per cent, depending on where the line between a normal and an abnormal record is drawn.

If one sets the number at 10 per cent, then one should expect, on the rules of chance, that throughout the population 1 per cent of married couples would both have dysrhythmia; that is, 1 of 10 men would marry 1 of 10 women and in 1 of 100 marriages both would have abnormal records. This would hold unless there is some unconscious selection of mates which brings two persons with dysrhythmia together. Because this genetic trait of the electrical activity of the brain is so closely concerned with the personality and the behavior of the person, an unconscious mental attraction based on the rhythms of the brain may not be as fantastic as it at first sounds. When both parents were examined we

found that in 35 per cent of the families both the father and the mother had pronounced dysrhythmia. This figure, which is thirty-five times as great as would be expected, indicates the importance of the presence of dysrhythmia in both parents. The importance of an inheritable trait in both parents has been emphasized by eugenists. It affords a means of minimizing the risk for patients with epilepsy who wish to have children. Without electroencephalographic examination, advice about the marriage of a person from an epileptic family is pure guesswork. Even a sibling of an epileptic person has nearly an even chance of not being a carrier, and the chance is much greater with more distant relatives. On the other hand, a person who has no family history of epilepsy has perhaps a 1 : 10 chance of being a carrier of this or an allied disorder. If the person with epilepsy will choose a mate who has a normal brain rhythm, his chance of having any offspring with epilepsy is greatly reduced. His chances of normal offspring are greater than those of parents both of whom have no present or family history of epilepsy but have brain waves of abnormal frequency. The chances cannot be stated in figures because of the lack of data.

If, as we believe, our data indicate that dysrhythmia is a dominant trait, then it cannot be "bred out" by mating with eurhythmic persons. Dysrhythmia will persist, unless society should assume the herculean task of universal electroencephalographic examinations and the elimination of offspring of the millions who have dysrhythmia. Because of the expense and training required for good electroencephalographic technic, suggestions which involve its widespread use may sound academic. On the other hand, the installation and operation of roentgen ray equipment was more difficult and more expensive; yet it has been accomplished. Probably dysrhythmia and its inheritance concern neuropsychiatric disorders other than epilepsy. This subject and its eugenic possibilities are of great importance to the nation as well as to the individual. Further studies should be extensive and should be carefully carried out and controlled.

SUMMARY

Electroencephalographic tracings have been made of the parents, siblings and children of 94 patients who had both clinical epilepsy and cerebral dysrhythmia. The relatives numbered 183. Tracings were made simultaneously from six areas of the cortex. Definitely abnormal records were obtained in 60 per cent of the relatives of patients and in 10 per cent of a control group of 100 persons who had no near relative with epilepsy. In 55 of the families records were obtained from both parents. In 35 per cent of these the records of both parents were definitely abnormal. In only 5 per cent were the records of both parents unmistakably normal. Dysrhythmia occurred as often among the rela-

tives of patients with so-called symptomatic epilepsy as among the relatives of patients with "essential" epilepsy. It occurred more often among the relatives of female (64 per cent) than of male patients (56 per cent) and more often among female relatives (65 per cent) than among male relatives (54 per cent). Females probably have more predisposition ("essential" epilepsy) than males. The data included 5 families in which there were similar twins with seizures or dysrhythmia. In each pair of twins there was a similarity of the fundamental rhythm, though seizures in both twins occurred in only 1 pair.

We believe this evidence indicates that the dysrhythmia of epilepsy is inheritable and that such a dysrhythmia when demonstrable may represent a predisposition to epilepsy or some allied disorder. Dysrhythmia may prove to be a dominant trait. Because approximately 2.4 per cent of the near relatives have epilepsy and approximately 60 per cent of relatives have dysrhythmia, persons with the predisposition to epilepsy or an allied disorder outnumber actual epileptic subjects by about 25 : 1. The incidence of epilepsy is about 0.5 per cent; hence persons with a predisposition to epilepsy form about 12 per cent of the population.

These observations should be of practical value in the prophylaxis and eugenics of epilepsy. They should assist the physician in tracing the descent of epilepsy and in advising patients and their relatives about marriage. The presence of dysrhythmia in both parents was thirty-five times the expected chance mating of two dysrhythmic persons. If a person with epilepsy marries, his chances of having epileptic offspring will be minimized if he chooses a person whose cortical electrical activity is normal.

NEUROLOGIC SIGNIFICANCE OF PLATYBASIA

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The relationship between certain craniovertebral skeletal deformities and associated neural changes, while discussed in the literature with respect to its various phases, seems more and more to be a manifestation of different aspects of the same process. Thus, there are interrelated elements of similarity binding together the conditions of platybasia (flattened base with deformity of the foramen magnum), occipitalization of the atlas, the Klippel-Feil [1] syndrome (defect of the atlas and sometimes fusion of one or more upper cervical vertebrae) and the Arnold-Chiari [2] malformation (lengthening of the pons and medulla, with herniation of the cerebellum into the spinal canal) in their relation to syringomyelic conditions, hydrocephalus and spina bifida. The significance of the Arnold-Chiari malformation in association with hydrocephalus and spina bifida has been discussed by Russell and Donald,[3] its appearance with hydrocephalus in the absence of spina bifida by McConnell and Parker [4] and the association of hydrocephalus with occipitalization of the atlas by Sinz;[5] the relationship between platy-

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1. Klippel, M., and Feil, A.: Un cas d'absence des vertèbres cervicales, Nouv. iconog. de la Salpêtrière **25**:223-250, 1912.

2. Arnold, J.: Myelocyste, Transposition von Gewebskeimen und Sympodie, Beitr. z. path. Anat. u. z. allg. Path. **16**:1-28, 1894. Chiari, H.: Ueber Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns, Deutsche med. Wchnschr. **17**:1172-1175, 1891. Schwalbe, E. S., and Gredig, M.: Ueber Entwicklungsstörungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina bifida, Beitr. z. path. Anat. u. z. allg. Path. **40**:132-194, 1907.

3. Russell, D. S., and Donald, C.: The Mechanism of Internal Hydrocephalus in Spina Bifida, Brain **58**:203-215, 1935.

4. McConnell, A. A., and Parker, H. L.: A Deformity of the Hind-Brain Associated with Internal Hydrocephalus: Its Relation to the Arnold-Chiari Malformation, Brain **61**:415-429, 1938.

5. Sinz, P.: Unterentwicklung des Hinterhaupt- und Keilbein-Körpers mit gleichzeitiger knöcherner Verbindung zwischen Atlas und Schädel als Todesursache, Virchows Arch. f. path. Anat. **287**:641-650, 1933.

basia and the Klippel-Feil deformity has been mentioned by Ebenius,[6] and the appearance of syringomyelia and hydromyelia in cases of the Arnold-Chiari malformation has been noted by D'Errico,[7] and in cases of platybasia by Chamberlain.[8] The present study concerns illustrative material of clinical, roentgenologic and pathologic nature with specific regard to platybasia.

Platybasia is a deformity of the base of the skull of unknown origin, affecting chiefly the foramen magnum. In this condition the foramen is pushed upward into the posterior fossa, and is usually small and misshapen and often eccentric, while the atlas as a rule becomes occipitalized. Because of the latter, the odontoid process of the axis frequently projects far into the cervical portion of the spinal canal, just below the foramen, and impinges on the brain stem, as described by Bézi.[9] Resultant neural changes may be produced singly or in combination by direct pressure, by reaction of the arachnoid to pressure, by pressure on the vertebral arteries of the rim of the foramen or by interference with escape of fluid from the foramens of Luschka and Magendie due to cerebellar herniation into the cervical portion of the canal. The bony deformity is said to have been first mentioned by Rokitansky in 1844, but it was described in detail by Virchow [10] in 1876 and by Grawitz [11] in 1880. Homén,[12] in 1901, discussed the association of this deformity with neurologic changes, with special reference to the role of the odontoid process; and Schüller,[13] in 1911, published the first definitive description of the whole matter. Schüller also described the roentgenographic appearance, as was done subsequently (in 1934) by Ebenius.[6]

Strangely, this complex, despite its apparently frequent relation to or simulation of such important entities as cervical syringomyelia, and possibly hydrocephalus, has gone virtually unnoticed in the Anglo-

6. Ebenius, B.: The Roentgen Appearance in Four Cases of Basilar Impression, Acta radiol. **15**:652-656, 1934.

7. D'Errico, A.: The Surgical Treatment of Hydrocephalus Associated with Spina Bifida, Yale J. Biol. & Med. **11**:425-430, 1939.

8. Chamberlain, W. E.: Basilar Impression (Platybasia), Yale J. Biol. & Med. **11**:487-496, 1939.

9. Bézi, I.: Assimilation of Atlas and Compression of Medulla, Arch. Path. **12**:333-357 (Sept.) 1931.

10. Virchow, R.: Beiträge zur physischen Anthropologie der Deutschen mit besonderer Berücksichtigung der Friesen, Berlin, G. Vogt, 1876.

11. Grawitz, P.: Beitrag zur Lehre von der basilaren Impression des Schädels, Virchows Arch. f. path. Anat. **80**:449-474, 1880.

12. Homén, E. A.: Zur Kenntnis der rhachitischen (?) Deformationen des Schädelbasis und der basalen Schädelhyperostosen. Deutsche Ztschr. f. Nervenh. **20**:3-15, 1901.

13. Schüller, A.: Zur Röntgen-Diagnose der basalen Impression des Schädels, Wien. med. Wchnschr. **61**:2593-2599, 1911.

American literature, except for articles such as Bézi's.[9] Chamberlain,[8] however, has recently revived interest in it. Five cases are reported, in all of which there were neurologic symptoms and roentgenographic verification, together with the operative, neurologic and pathologic observations.

REPORT OF CASES

CASE 1.—*Platybasic abnormality of the foramen magnum with syringomyelic changes. Operation. Observation and relief of foraminal constriction and herniation of right cerebellar tonsil. Improvement.*

History.—F. R., a man aged 49, was admitted to the Illinois Research and Educational Hospitals on Sept. 23, 1938, with marked weakness and numbness of the upper extremities. The past history revealed no factors contributing to the present illness. The patient was married and had 3 children.

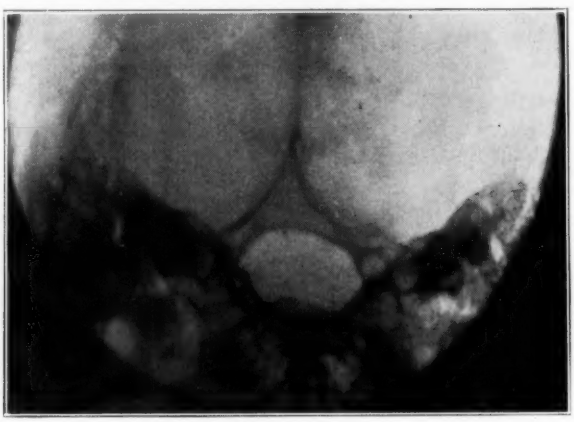

Fig. 1 (case 1).—Flattening of the foramen magnum.

Present Illness.—Three years previously the patient noticed a bleeding sore on his right shoulder on awakening in the morning. He particularly noticed that there was no pain associated with it. Shortly after this, both arms and shoulders became weaker than they had been, the right ankle and knee being weaker than the left. At about the same time he noticed wasting of the muscles of the right shoulder. He stated that one year later his right hand and arm became numb and the extremity useless.

Examination.—The findings were limited to the thorax and extremities. There were: absence of pain and temperature sense over the second, third, fourth and fifth cervical segments bilaterally; loss of touch sensation over the fifth cervical area on the right, with loss of vibratory sensation in the right upper extremity and diminution in the left upper extremity; marked muscular atrophy, with pronounced weakness, of the right shoulder girdle and the right arm, and increase in deep reflexes on the right with a positive Hoffmann sign on that side.

The laboratory findings and the spinal fluid dynamics were normal.

The diagnosis of syringomyelia was made, and the patient was given 3,500 r to the cervical and dorsal portions of the spine, without improvement.

Roentgenograms taken on Nov. 15, 1939 showed an abnormal foramen magnum.

On Nov. 22, 1939 the patient was readmitted to the hospital. Examination revealed no progression of symptoms. The following changes were observed bilaterally: subjective numbness and paresthesias of the upper and lower extremities; anesthesia to pain and temperature sense from the second cervical to the first dorsal segment, inclusive, and over the fifth lumbar and first sacral segments; absence of the triceps jerk, with atrophy of the shoulder girdle on the right side, and increased knee and ankle jerks.

Operation (Dec. 6, 1939).—Decompression of the foramen magnum was performed. Marked vascularity of the bone was encountered in the procedure. The lamina of the first cervical vertebra was removed. The dura seemed constricted in the region of the foramen. On opening the dura, the right cerebellar tonsil was observed to be herniated below the level of the first cervical vertebra. The left cerebellar tonsil was normal. The right cerebellar tonsil was bound down with adhesions; these were freed and the tonsil was mobilized. The wound was closed with the dura left open.

Course.—After operation atelectasis developed, but the patient recovered and was discharged on the twenty-eighth postoperative day.

Jan. 22, 1940: Reexamination showed the anesthetic area to be restricted to the second, third and fourth cervical segments bilaterally. There was no paresthesia in the lower extremities. All sensation had returned to both hands, and there seemed to be some return of strength and development of the muscles of the right shoulder.

May 27: The lower extremities were normal, with no pain. Pain sensation was present to a moderate degree in the upper extremities, with some paresthesia. An area of anesthesia extended from the second to the fourth cervical segment bilaterally. The patient was working as a laborer, which occupation he had been forced to give up four years previously.

CASE 2.—*Typical platybasia with abnormality of the foramen magnum and syringomyelic changes. Operation, with observation and relief of foraminal constriction and foraminal herniation of both cerebellar tonsils.*

History.—D. C., a man aged 26, entered the surgical service of the Peter Bent Brigham Hospital in April 1931, with the complaint of dragging the right leg while walking for seven years, together with paresthesia of both hands and marked weakness of the right hand for an equal length of time. The symptoms had all progressed insidiously from the onset.

The past history revealed no factor contributory to his present illness.

Examination.—This showed: inequality of the pupils, the right being larger than the left; nystagmus in all directions; atrophy and definite weakness of the right arm and leg; atrophy of the right side of the tongue; hypotonicity of both arms, with spasticity of both legs; hypesthesia from the second cervical to the eighth thoracic segment and on the right side from the second cervical to the fifth thoracic on the left; hypalgesia over the right side of the face, and absence of deep reflexes at the elbows, with increased knee and ankle jerks and a positive plantar response bilaterally. There was a high color index of the blood. Lumbar puncture revealed a partial block.

Operation (May 8, 1931).—A cervical laminectomy was performed by Dr. Harvey Cushing. The laminas were removed from the fourth, fifth and sixth cervical vertebrae; it was observed that the cervical portion of the canal was definitely widened, and the cervical portion of the cord bulging and cystic. An

attempt was made to enucleate the cyst, but was given up because of the vascularity. The cyst was punctured and found to contain clear spinal fluid.

Course.—After operation the findings were the same as before except for a slight degree of choking of the disks, which had cleared up at the time of discharge. The neurologic findings remained the same as before operation.

The patient then returned home and carried on office work until Jan. 4, 1937. He stated that during the interim his symptoms progressed slowly, but did not incapacitate him. He then entered St. Luke's Hospital, Chicago; neurologic examination revealed the following changes in the signs previously observed: equality of the pupils and absence of nystagmus; protrusion of the tongue normally in the midline, with no atrophy; anesthesia to pain, temperature and touch sensa-

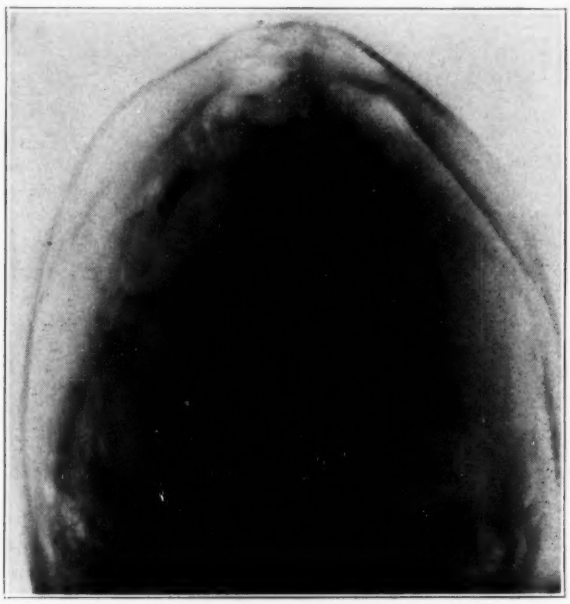

Fig. 2 (case 2).—Deformity of the foramen magnum.

tion from the second cervical to the eleventh thoracic segment on the right and to the tenth thoracic on the left, and generalized hypesthesia over the dorsal and lumbar regions. Roentgen therapy was ordered, but the patient stated he could not notice any improvement.

May 16, 1938: On admission to the Illinois Research and Educational Hospitals, neurologic examination revealed partial loss of power, with atrophy, on the right side of the body; anesthesia to pain, temperature and touch sensation from the second cervical to the second lumbar segment bilaterally, and marked spasticity of the lower extremities with positive plantar responses. There was now paralysis of the twelfth nerve on the left side. The patient also had scoliosis, which had not previously been noted. He then received 1,400 r over the cervical region of the cord, with no objective improvement. Slow progression of symptoms continued until January 1940.

Jan. 3, 1940: On entrance to St. Luke's Hospital, there were the additional findings of right foot drop, absence of paralysis of the twelfth nerve and complete inability to use the right arm, though slight movement was present. Roentgenograms showed occipitalization of the first cervical vertebra with definite encroachment of the foramen magnum in the anterior half on the right side.

Operation (January 5).—Operation revealed marked thickening of the bone in the occipital region with an asymmetric occipital protuberance. The bone was removed in the region of the foramen magnum, giving a wide decompression. The first cervical vertebra was delaminated. The dura was observed to be thickened and constricted at the foramen. On opening the dura down to the second cervical vertebra, both cerebellar tonsils were seen to have extended into the cervical portion of the canal down to this vertebra. They were bound down by adhesions, which were carefully freed and the tonsils mobilized, but not amputated. The wound was closed, with the dural decompression.

Postoperative convalescence was uneventful except for the flaring up of an old infection of the bladder, which was easily controlled. At the time of discharge from the hospital the patient thought he was improved.

The patient has not been checked neurologically since operation, but from his correspondence we have received the information that he has returned to his work as an insurance salesman and that there is some improvement, though slight.

These 2 cases illustrate the concomitant appearance of platybasia and syringomyelia-like symptoms and lesions. In both cases, in addition to the foraminal deformity, there was cerebellar herniation into the cervical part of the canal, such as is found in the Arnold-Chiari malformation. In case 3, in which complete clinical and postmortem studies were made, the chronic medullary embarrassment and interference with circulation of fluid between the posterior fossa and the spinal subarachnoid space seem to have been caused by the direct pressure produced by the platybasia and the accompanying odontoid projection per se.

CASE 3.—*Typical platybasia with dilatation of the ventricles, hydromyelia of the proximal portion of the cord and true syringomyelia of the distal portion. Operation. Death four months later from urinary infection. Autopsy.*

History.—Mrs. Sally B., a Negress aged 46, was admitted to the Illinois Research and Educational Hospitals on Feb. 24, 1937, with marked weakness of the upper extremities.

The past history gave no significant factors which might have a bearing on the present condition. She was married at the age of 27, and had four pregnancies, with no miscarriages or stillbirths. One child had died of an intestinal obstruction.

Present Complaint.—There was weakness of both hands and arms, of two years' duration. The symptoms progressed insidiously and were not relieved. Shortly after the onset of the weakness in the hands, the left foot began to drag and progression of weakness was similar to that in the arms. One year later numbness began in both hands, more severe in the right. The numbness progressed slowly down the right side of the body and involved the right leg, although not as completely as the right arm. About eight months after the first onset of numbness, the left side of the face became numb.

Examination.—There were bilateral ptosis, inequality of the pupils and nystagmus to the left, with paralysis of convergence of the left eye; hypesthesia of the left side of the face, with anesthesia of the left cornea; weakness of the muscles of mastication on the left side; deviation of the palate to the left; weakness of the right sternocleidomastoid and trapezius muscles; deviation of the tongue to the right, with atrophy and fibrillation; practically complete spastic paralysis of both arms and partial spastic paralysis of the left leg; marked atrophy of the thenar and hypothenar eminences, together with contractures of both hands; absence of pain, temperature and touch sensation over the entire right arm and right side of the thorax from the third cervical to the sixth thoracic level; diminished pain and temperature sensation over the right leg and right side of the abdomen; absence

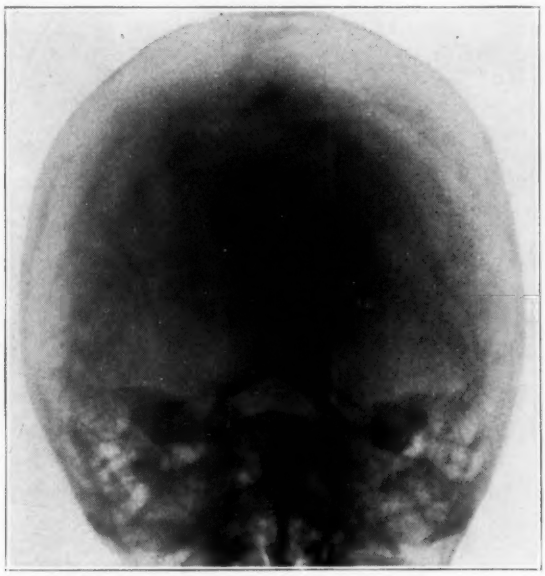

Fig. 3 (case 3).—Deformity of the foramen magnum.

of vibratory sensation in all extremities; absence of the right biceps and triceps reflexes, with exaggeration of the rest of the deep reflexes, and absence of superficial reflexes.

The laboratory findings were all normal, as were the spinal fluid dynamics. A diagnosis of syringomyelia with syringobulbia was made. The condition was considered too far advanced for roentgen therapy.

Interval History.—All symptoms progressed slowly while the patient was under observation in the dispensary. She was readmitted to the hospital in January 1940. The additional symptoms at this time were marked contractures in flexion of both arms and very marked atrophy of both arms. The deep reflexes were all absent except for ankle clonus on the left side. Roentgen examination of the skull revealed occipitalization of the first cervical vertebra with marked decrease in the anteroposterior diameter of the foramen magnum and definite abnormality in its size and shape. A diagnosis of platybasia with syringomyelia and syringobulbia was made.

Operation (Jan. 31, 1940).—Decompression of the foramen magnum was done, with removal of the laminas of the first and second cervical vertebrae. The first cervical arch was practically fused to the occipital bone. On exposure of the dura there was observed an apparent constriction at the level of the foramen with marked thickening of the dura itself. The dura was opened down to the third cervical vertebra, and the cord was observed to be smaller than normal in this area.

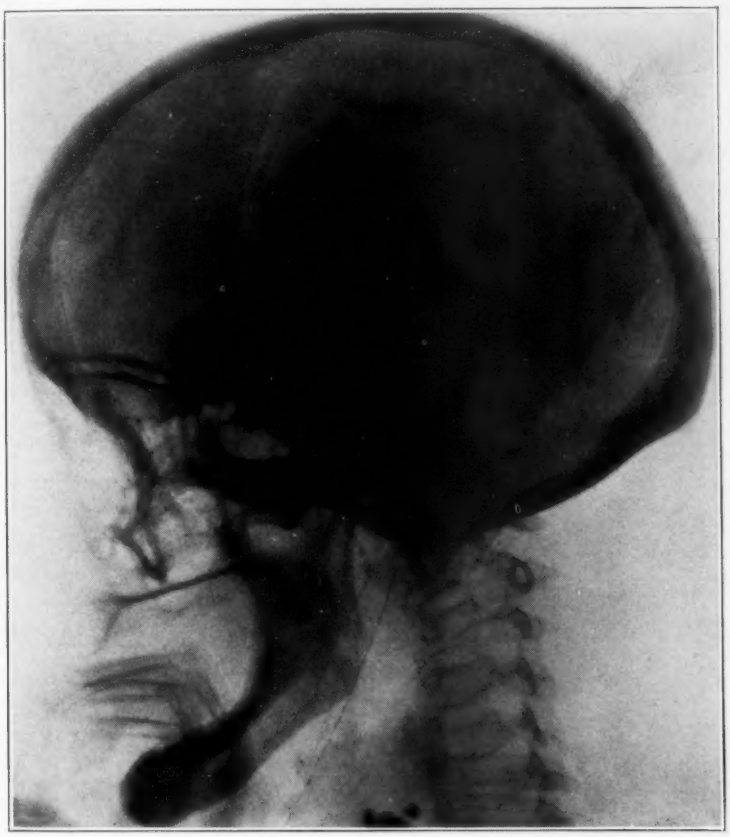

Fig. 4 (case 3).—Occipitalization of the atlas.

Postoperative convalescence was not unusual, and the patient was discharged to return home on the twentieth postoperative day. At the time of discharge the patient thought she noted improvement, but we were unable to evaluate this neurologically. After her return home cystitis and pyelitis developed, and she died on April 24, 1940.

Autopsy.—Examination was confined to the brain and spinal cord. The pathologic changes consisted of definite constriction of the cervical portion of the cord opposite the foramen magnum, slight internal hydrocephalus and a syringomyelic cavity which extended downward from the fourth cervical segment to the

end of the cord. Microscopic sections through the area of constriction and the adjacent regions revealed hypertrophy of the ependymal cells lying in the central canal, with dilatation of the fourth ventricle extending downward to the area of constriction. Beginning in the lower cervical portion of the cord, a true syringo-

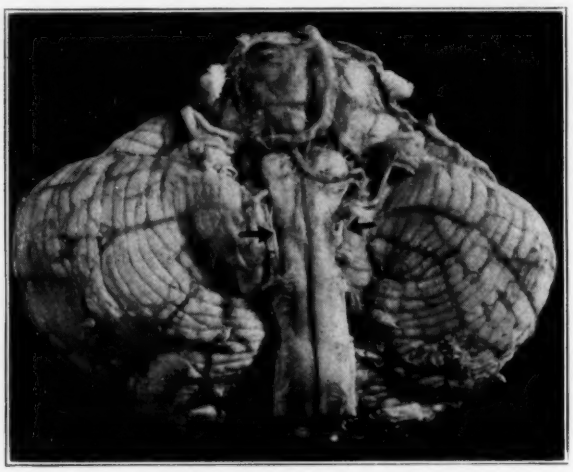

Fig. 5 (case 3).—Constriction of the medulla.

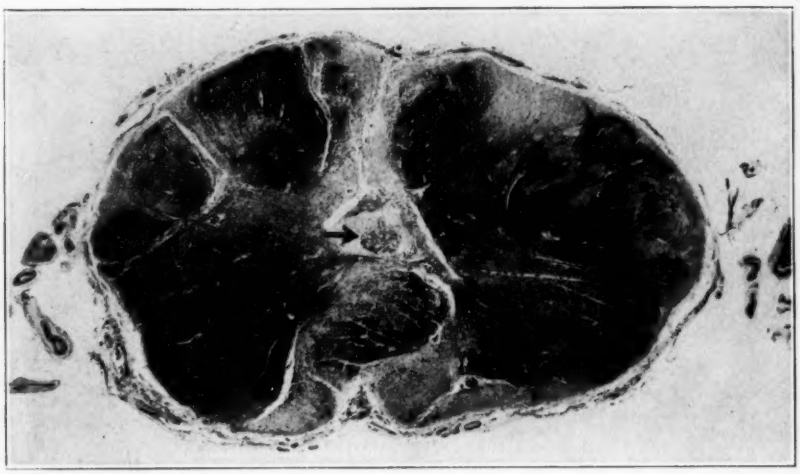

Fig. 6 (case 3).—Section through the brain stem at the point of foraminal constriction, showing ependymal proliferation. Weil stain.

myelic cavity extended distally throughout its length. The odontoid process protruded 8 mm. into the canal against a thickened pad of dura and scar tissue corresponding in size to the odontoid process, which was immediately opposite the area of constriction of the cord.

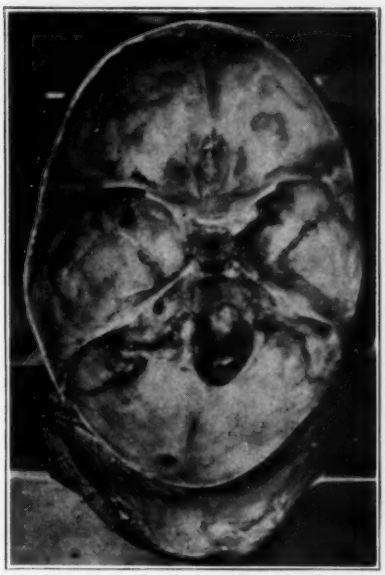

Fig. 7 (case 4).—Asymmetry of the base of the skull, with deformity of the foramen magnum.

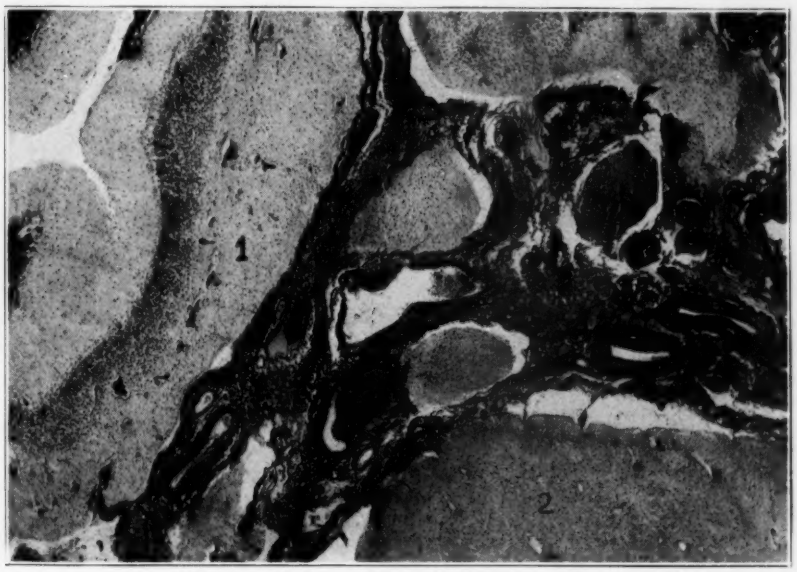

Fig. 8 (case 4).—Dense leptomeningeal proliferative adhesions between the cerebellum (*1*) and the brain stem (*2*). Van Gieson stain.

The next case is illustrative of the manner in which an odontoplatybasic obstruction may be associated with, and possibly responsible for, internal hydrocephalus.

CASE 4.—*Platybasia with internal hydrocephalus. Ventricular exploration. Death. Autopsy.*

History.—R. G., a boy aged 4 years, was admitted to the Illinois Research and Educational Hospitals on Oct. 22, 1939, with marked hydrocephalus and difficulty in moving the right side of the body.

The past history did not reveal any diseases of childhood or other illness, aside from enlargement of the head since birth.

Present Illness.—The mother noticed enlargement of the head at birth, and this had progressed up to the date of entrance to the hospital. There had been difficulty in handling the right leg during the past two months, together with nausea, vomiting and headaches. Marked drowsiness had been present for the past two weeks.

Examination.—This revealed enlargement of the head; secondary optic atrophy, but no other abnormalities of the cranial nerves; loss of motor power in the right leg, with a positive plantar response and spasticity, and drowsiness. A presumptive diagnosis of tumor of the third ventricle, possibly in the nature of a cholesteatoma, was made.

Operative Procedure (October 25).—A ventriculogram showed greatly increased intracranial pressure and marked internal hydrocephalus. Exploration of the third ventricle, which followed, revealed no tumor. The patient died five hours after the procedure. Reexamination of the roentgenograms of the skull revealed an eccentric foramen magnum, with decrease in the anteroposterior diameter and irregularity.

Autopsy.—Postmortem examination revealed eccentricity and flattening of the foramen magnum with marked protrusion of the odontoid process into the cervical portion of the canal on each movement of the head. There was internal hydrocephalus with dilatation of the aqueduct and the fourth ventricle. There were marked adhesions around the foramen magnum.

Case 5 is reported chiefly to demonstrate the lack of any distinct borderline between the syringomyelic status which obtains in the Klippel-Feil deformity and that which occurs in platybasia. In view of the observations in the other cases, an exploration of the posterior fossa in this case might well have revealed arachnoid adhesions at the foramen.

CASE 5.—*Abnormal foramen magnum with a modified Klippel-Feil abnormality and syringomyelic lesions. Operation.*

History.—M. B., a man aged 25, was admitted to the hospital on Nov. 8, 1939, with marked weakness and numbness of the upper extremities.

There was no history of factors contributing to the present illness.

Present Illness.—After an attempt to lift a heavy weight in 1935, numbness, followed by paralysis, of the left arm developed. There was functional recovery after two years.

The patient was well until November 1938, when he was knocked unconscious by a blow under the right eye; eight days later numbness and weakness of the right arm developed. The weakness grew progressively worse until his entrance to the hospital.

Examination.—There were atrophy and paralysis of the supraspinatus, infraspinatus, deltoid and triceps muscles on the right. There was also atrophy of the thenar and hypothenar eminences on that side. There were anesthesia over the sixth and seventh cervical segments on the right side and absence of reflexes in the right arm. The rest of the neurologic examination gave normal results. Roentgenograms of the foramen magnum showed an erosion of the occipital bone with suspicious involvement of the first cervical vertebra. Lumbar puncture revealed a partial block.

Operation (Nov. 30, 1939).—There was marked asymmetry of the patient's head, and the posterior edge of the foramen magnum was virtually absent on the left side, as was almost all the arch of the atlas, particularly on the left side. The entire region was well exposed, including the occipital bone and the upper

Fig. 9 (case 5).—Deformity and partial absence of the foraminal rim and the arch of the atlas.

four cervical vertebrae. The second, third and fourth vertebrae were then delaminated and the defective first vertebral arch was widened. The dura was opened; this revealed enlargement of the spinal cord. Careful inspection of the entire region revealed no other abnormality, and it was believed at the time of operation that the appearance of the cord did not sufficiently resemble that of syringomyelia to warrant puncture.

Postoperative convalescence was uneventful, and the patient was discharged as improved.

COMMENT

A consideration of the foregoing cases makes it apparent that there may well be a connection between the craniovertebral skeletal deformity known as platybasia and hydrodilatation and malformation of the central nervous system, resulting in internal hydrocephalus when the acute obstruction occurs in early life and in hydromyelia or other disturbances when it exists chronically in later life. When such obstruction

occurs, it is probably due to two chief sources acting in combination: actual constriction of the brain stem and its membranes, both of its intrinsic tissue and of its blood supply and also of the column of fluid surrounding it; and interference, mild or severe, with the flow of cerebrospinal fluid between the spinal canal and the intracranial cavity, caused by reactive arachnoid adhesions or by occlusion of the normal exits from the fourth ventricle because of cerebellar herniation through the foramen magnum.

It makes no difference which of two hypotheses one accepts: the theory substantiated by the successive and interdependent contributions of Faivre,[14] von Luschka [15] and Dandy,[16] that the cerebrospinal fluid is elaborated chiefly by the choroid plexus in the lateral ventricles and escapes through the ventriculosubarachnoid system via the foramens of Luschka and Magendie, to be absorbed by the arachnoid villi; or the theory of Hassin [17] that the fluid is a tissue juice which leaves this system through the foramens of the craniospinal nerves. In either case, free access from the cranial to the spinal cavity and unimpeded flow from the ventricular to the subarachnoid space are necessary to the preservation of normal dynamics. In a condition like platybasia, associated, as it sometimes seems to be, with cerebellar dislocations of the Arnold-Chiari pattern, there is such an interference with the normal circulation of fluid. When to this is added the natural glial reaction to pressure, adhesions and deficient blood supply, it does not seem presumptuous to assume an etiologic relationship between the skeletal deformity and many at least of the associated neurologic conditions. At any rate, it appears that good judgment dictates roentgenographic examination of the upper cervical portion of the spine and the foramen magnum in every case in which the malformation is suspected, and that surgical decompression and lysis of the structures lying immediately above and below the foramen have at least theoretic possibilities of benefit.

CONCLUSIONS

1. Five clinical examples of roentgenologically verified deformity of the foramen magnum are described in which there were concomitant neurologic findings resembling, in the 4 adults, those of syringomyelia and, in the child, those of hydrocephalus with destruction of the brain.

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14. Faivre, J. J. A. E.: Des granulations méningiennes, Thesis, Paris, no. 142, 1853.

15. von Luschka, H.: Die Adergeflechte des menschlichen Gehirns, Berlin, G. Reimer, 1855.

16. Dandy, W. E.: Experimental Hydrocephalus, Tr. Am. S. A. **37**:397-428, 1919.

17. Hassin, G. B.: Hydrocephalus: Studies of the Pathology and Pathogenesis, with Remarks on the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **24**:1164-1184 (Dec.) 1930.

In all the cases operation was performed. Two patients died, 1 of subsequent urinary infection and the other after operation; in both hydrocephalus, of different degrees, was observed post mortem. One patient has improved markedly since operation. The other 2 patients have had too short a postoperative interval for evaluation of results. The operative and postmortem observations and the pathologic material are described and illustrated.

2. The mechanism by which platybasia may produce neural damage is discussed, and its relationship to the Klippel-Feil syndrome and the Arnold-Chiari malformation is indicated. It is possible that the changes in the spinal cord observed in these conditions may have an explanatory bearing on the confusion which exists in the controversy over the true nature of primary syringomyelia.

3. Routine roentgen examination of the foramen magnum and upper cervical portion of the spine is suggested in all cases in which a diagnosis of cervical syringomyelia and in some cases in which a diagnosis of chronic hydrocephalus has been made.

4. Surgical therapy in positive cases, with decompression of the foramen magnum, freeing of foraminal adhesions and occasionally amputation of the cerebellar tonsils, is advocated.

ABSTRACT OF DISCUSSION

DR. TRACY J. PUTNAM, New York: The series of cases which the authors have reported is an interesting illustration of the fact that congenital abnormalities are apt to occur in groups. There are certain predilections among these groups. Hydrocephalus and spina bifida are frequently found to be associated; somewhat less often, hydrocephalus and abnormalities of the surface of the brain; very often, hydrocephalus and abnormalities of the posterior fossa, as well as web fingers, polydactylism and deformities elsewhere in the body. It appears that if anomalies occur in one germ layer in one segment they are apt to occur in the same germ layer in other segments, although they are not necessarily confined to this germ layer.

This is an important condition to recognize. Surgeons have also had the experience that operation in cases of such anomalies is occasionally attended with a fair degree of relief, which sometimes does not seem to be explained by what has been done. I think one might raise the question whether opening the cerebrospinal cavity might not be indicated in more of these cases. Roentgen treatment is sometimes effective, even when one is faced with deformities in addition to syringomyelia.

I should like to ask Dr. Oldberg whether he has any explanation for the late onset of symptoms in many cases of what apparently is a congenital, probably hereditary, defect.

I wish he would say more also about the presumed mechanism of hydrocephalus in these cases. Dr. Oldberg and Dr. Hassin recently published a paper on this subject (Hassin, G. B.; Oldberg, E., and Tinsley, M.: Changes in the Brain in Plexectomized Dogs, with Comments on the Cerebrospinal Fluid, ARCH.

NEUROL. & PSYCHIAT. **38**:1224 [Dec.] 1937), from which I gathered that they believe that obstruction to the outflow from the ventricular system would not be expected to produce hydrocephalus.

DR. LEO M. DAVIDOFF, Brooklyn: I think the importance of this contribution lies in the fact that by application of the principle of the interrelationship of the brain and the spinal cord to their bony envelope the authors have been able to bring together apparently unrelated syndromes and have demonstrated that they have certain things in common. If one keeps in mind that at least during the growth period of the organism this interrelationship of the brain and spinal cord to the skull and spine is a dynamic one, it is easy to see how they have made the application.

Several years ago an opportunity was given me to examine a large series of roentgenograms in the collection of the late Prof. T. Wingate Todd, of Western Reserve University School of Medicine, taken of normal children whom he had examined repeatedly from birth until the age of 18 or 20. By examining these roentgenograms of the skull, it was possible to see how from birth the effect of the growth of the brain had registered itself on the skull, with the convolutional impressions of various degrees on the inner table. While this is the normal relation, the moment something abnormal takes place in the nervous system, on the one hand, or in the skull and spinal canal, on the other, the one affects the other. As an example may be cited the case of oxycephaly, in which there is premature closure of the sutures of the brain; in this condition there is immediately a marked increase in the convolutional markings, due to the fact that the skull does not give way in the normal manner to the growth of the brain; and frequently there are secondary effects—for example, atrophy of the optic nerves.

The reverse may occur in a situation such as a birth injury affecting half the brain, in which case there is shrinkage of the brain substance but a corresponding change in the bony capsule in the opposite direction, namely, thickening of the skull with dilatation of the air sinuses to fill the space which failure of the brain to grow normally has left vacant.

In applying a principle of this sort, it is possible to do as the authors have done—bring together a large number of what seem to be unrelated conditions with perhaps various etiologic factors and, having subjected them to this principle, work out a form of surgical therapy that may be of benefit in these conditions, which otherwise have been considered unamenable to any form of treatment.

DR. ERIC OLDBERG, Chicago: As Dr. Putnam has said, the surgical treatment of the rather hopeless condition of syringomyelia has previously consisted of splitting the posterior columns and draining the syringomyelic cavity. Therefore, a new understanding of the causes underlying the condition represents an advance in therapy, in that one may surgically unblock the normal fluid pathways between the cranial and the spinal cavity, and between the intracranial ventricular and the subarachnoid spaces.

In answer to the question why the neurologic manifestations of a congenital condition may appear as late as the third or fourth decade, I should say it is conceivable that for years the central nervous system may be able to compensate for the mild chronic interference with normal fluid dynamics, but that finally the compensation breaks.

ELECTROENCEPHALOGRAMS OF "CONSTITUTIONALLY INFERIOR" AND BEHAVIOR PROBLEM CHILDREN

COMPARISON WITH THOSE OF NORMAL CHILDREN AND ADULTS

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The importance of the electroencephalogram as a clinical and experimental tool is constantly being demonstrated. Clinically, its most important applications have been in the diagnosis and study of epileptic and related conditions and in the discrimination and localization of tumors of the brain. Abnormal signs of other neurologic and psychiatric disorders have been recognized and studied, but so far with less marked success. One reason for this seems to be that there is a need for more detailed methods of analysis and quantification of records as well as the establishment of standards based on large numbers of so-called normal subjects.

Experimentally, the correlation of the electrical activities of the brain with the functions of its various parts is being prosecuted chiefly in animals, and on this work much of the interpretation of the human electroencephalogram will ultimately depend. Important experimental contributions are also being made in the study of human electroencephalograms in relation to a variety of normal and abnormal physiologic conditions (such as metabolism, acid-base balance and sleep), developmental aspects as a function of age and the influence of drugs on the central nervous system.

The present study is an attempt to supply additional standards based on detailed analyses of records from normal subjects, but more particularly to demonstrate that the electroencephalograms of the normal subjects differ significantly from those of behavior problem children and a group of "constitutionally inferior" children. Reports of previous studies [1] from this laboratory have discussed abnormalities in the electroencephalograms of behavior problem children.

From the Emma Pendleton Bradley Home.
This research was aided by a grant from the Rockefeller Foundation.

1. Jasper, H. H.; Solomon, P., and Bradley, C.: Electroencephalographic Analyses of Behavior Problem Children, Am. J. Psychiat. **95**:641-658, 1938. Cutts, K. K., and Jasper, H. H.: Effect of Benzedrine Sulfate and Phenobarbital

(Footnote continued on next page)

MATERIAL AND METHODS

Normal Children.—This group consisted of 36 children (14 boys and 22 girls) who were apparently in good health and had no known history of serious illness likely to affect the central nervous system. These children were selected from a middle class population, the only selective factor being an attempt to cover the age range of 7 to 13 years fairly evenly with boys and girls, so that comparisons could be made with the other groups of children. To our knowledge the subjects were all from good homes and environments and were not recognized as presenting any problem in behavior or management. Although intelligence quotients were not available for this group, it seems safe to estimate on the basis of their behavior and scholastic level that all were of average intelligence or above.

College Students.—This group of young adults consisted of 30 upper class students (18 men and 12 women) from Brown University, all of whom appeared to be healthy. Their scholastic rank attests to the fact that they were of high average or superior intelligence These subjects were included partly to provide additional adult norms and partly as a control group in which the factor of maturity and its possible effects on the electroencephalogram might be evaluated in a comparison with the results in the group of normal children.

Behavior Problem Children.—In this group there were 50 children (44 boys and 6 girls) evenly distributed between the ages of 7 and 13 years who had been referred to the Emma Pendleton Bradley Home as presenting behavior problems. Their histories gave evidence of behavior difficulties, at home, at school or in the community, of sufficient degree to warrant their admission to the hospital for special study. These 50 children were selected from a larger group of behavior problem children on the basis of essentially normal physical and neurologic findings. All behavior problem children with a history of convulsions or other physical or neurologic symptoms which might be related to their behavior disorder were omitted from this group. The average intelligence quotient for the group was 98, with a range of 69 to 132.

The behavior problems represented in this group were of wide variety and consisted of such factors as hyperactivity, irritability, restlessness, temper tantrums, lying, stealing, truancy, obscenity, running away from home and defiance of authority to the extent of unmanageability in the home or delinquency in the community. It should be emphasized that the majority of the children were from the low or middle economic classes. In most cases there were unfavorable environmental factors either in the home or in the community, but in many instances there were siblings making fairly satisfactory adjustments under the same circumstances.

"Constitutionally Inferior" Children.—This group consisted of 30 children from 5 to 13 years of age, but for purposes of comparison with the other groups of children the data for only 22 of them (15 boys and 7 girls), ranging from 7 to 13 years of age, are presented. For want of a better or more precise classification this group has been called "constitutionally inferior." This may not be justified, but it is apparent that in general they had a very poor heritage, biologic, social, economic or medical. They were all wards of the state and for the most part

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on Behavior Problem Children with Abnormal Electroencephalograms, Arch. Neurol. & Psychiat. **41**:1138-1145 (June) 1939. Lindsley, D. B., and Bradley, C.: Electroencephalography as an Aid to Understanding Certain Behavior Disorders of Childhood, Ztschr. f. Kinderpsychiat. **6**:33-37, 1939.

had been found by social agencies to be unplaceable in foster homes. An average intelligence quotient of 88 (range of 61 to 113) indicates that as a group they were of dull normal or very low average mental ability. Only those abbreviated physical examination of whom gave negative results were used as subjects.

APPARATUS AND PROCEDURE

Four amplifying and recording channels made possible simultaneous recording from four regions of the head. The recording units consisted of a four pen ink-writing oscillograph (crystal) and a Westinghouse four element mirror oscillograph, which could be operated simultaneously. The data presented here were derived entirely from the ink writer records, the photographic records taken at random intervals during the continuous ink writer recording being used primarily as indicators of the accuracy of detail. The amplifiers were of the push-pull type throughout and had a time constant of approximately one second. They were operated at sufficient sensitivity to make 3 microvolt signals detectable and measurable.

The routine electrode placement was as follows: Fourteen electrodes were attached over bilaterally homologous regions of the head, with pairs over the occipital, central and frontal regions and a so-called indifferent electrode over each mastoid process. The electrodes of each pair were 2.5 cm. apart, except when a so-called monopolar system (lead over the mastoid process to one of the occipital, central or frontal leads) of recording was followed. Both the "bipolar" and the "monopolar" system of recording were used, but analysis only of "bipolar" records is presented here. It was believed that the "bipolar" records gave a more localized and discriminative picture of the activities of the different regions of the head. The "monopolar" records were always of greater magnitude by about twofold and gave essentially the same pattern of activity in the occipital regions, but introduced a more prominent alpha component in the central and frontal regions than was characteristic of these regions in "bipolar" records. The "bipolar" records, therefore, gave a clearer picture of the nonalpha activities of the central and frontal regions.

Small silver electrodes in the shape of hats with felt brims and coated with silver chloride were used. Electrode jelly was inserted through a hole in the top of the electrodes. The electrodes were attached by means of collodion. The interelectrode resistance was reduced to a minimum and equated for each pair of electrodes.

The subject lay, with eyes closed, on a cot in a partially lighted and relatively soundproof room. An observer sat beside the subject and signaled all observable movements of eyes or other body parts. A recording period lasted from twenty to forty minutes, with records from all regions of the head systematically distributed throughout. Frequent brief periods of rest allowed the subject to stretch or readjust himself and talk to the observer. This tended to put him at ease and to relieve any tensions or anticipations he may have had at the start.

After several series of records the observer instructed the subject how to hyperventilate or overbreathe at a relatively uniform depth and constant rate. After a short control record hyperventilation was begun, the observer signaling each respiration. Hyperventilation was continued for one to one and one-half minutes unless a marked "effect" appeared before that time, in which case the subject was told to stop overbreathing and remain quiet until the records returned to their original state.

METHODS OF ANALYSIS OF RECORDS

As a standard procedure, 3 meters of record, amounting to one hundred seconds in duration, was selected for analysis, 1 meter being taken from each third of the twenty to forty minute period of recording. This provided representative samples from the occipital, central and frontal regions throughout the period of recording. Preliminary to beginning the analysis a survey of the entire record was made to determine roughly what rhythmic groups or types of waves were present. Three or more waves in rhythmic sequence were taken to represent a rhythm if they had a relatively common pattern, amplitude and duration, but isolated waves of the same duration were also included in the measurements.

Ten or more nonconsecutive groups of 10 alpha waves in sequence were selected at random throughout the 3 meters of record and measured in millimeters, the average of these measurements being converted into the frequency per second. Amplitude was determined for the first 100 alpha waves of each meter sample by marking off the peak to trough height of each wave on a piece of paper tape. The average amplitude for the 300 waves was converted into peak microvolts. The per cent of time that alpha waves were present in the three 1 meter samples was determined by moving a piece of transparent celluloid, marked with the longest and shortest alpha wave durations, along each meter of record, any waves which fell outside the alpha range being thus eliminated. Measurements of amplitude could be made with considerable accuracy to a lower limit of 3 microvolts, and measurements of the per cent of time each type of wave was present therefore could also be extended to this level. With the exception of some of the adult records, which were of low amplitude in the central and frontal regions, the values were usually well above the lower limit.

The analysis with respect to the other types of waves was carried out in essentially the same way, except when waves were not plentiful. In such cases determinations of frequency and amplitude were made on as many groups of rhythmic waves as were available in the samples. If these proved too few for an adequate sampling, other sections of the records were examined.

Measurements During Hyperventilation.—Overbreathing in some cases produced what we have called a "hyperventilation effect." This is defined as a distinct change (usually abrupt) in the electroencephalogram, consisting of a sequence of slow waves, ranging in frequency from 2 to 8 per second and usually of a magnitude considerably above anything of similar frequency occurring in the records before hyperventilation. The "hyperventilation effect" may persist as a continuous series of rhythmic slow waves or may consist of repeated bursts of slow waves at irregular intervals. Two measurements were made, one of the duration from the beginning of hyperventilation to the onset of the "effect," the other of the duration from the cessation of hyperventilation to the disappearance of the "effect."

RESULTS

Detailed analyses of the records from the right occipital, central and frontal regions for all groups of subjects are presented in tables 1, 2 and 3.

The data are arranged according to frequency bands, which seemed to form natural divisions and allow for classification of all rhythms encountered. Waves below 2 per second were not seen in the records of any of the subjects included in this study, although they have been found in a few cases of neurologic disorders which we have studied.

TABLE 1.—*Analysis of Occipital Electroencephalograms in Terms of Distinguishable Frequency Bands, Showing Frequency per Second, Amplitude in Microvolts, Per Cent of Time Present and Number and Per Cent of Subjects Showing More Than 5 per Cent of Each*

Frequency Bands	Normal Children No.: 36 Ages: 7-13	Behavior Problem Children No.: 50 Ages: 7-13	Constitutionally Inferior Children No.: 22 Ages: 7-13	College Students No.: 30 Ages: 18-30
2 to 5				
Frequency	4.6 (4.2-4.9)	4.4 (3.0-5.1)	4.5 (2.6-5.3)	None
Amplitude	23 (9-42)	27 (14-42)	31 (5-56)	
Per cent of time present	11 (5-44)	17 (5-31)	16 (5-35)	
Number of subjects	7 (19%)	18 (36%)	5 (23%)	
5 to 8				
Frequency	5.9 (5.3-6.5)	6.2 (4.9-7.2)	6.5 (4.9-7.6)	6.5 (5.2-7.7)
Amplitude	16 (10-24)	23 (13-33)	20 (10-37)	17 (14-20)
Per cent of time present	10 (5-27)	14 (5-43)	17 (5-59)	6 (3-10)
Number of subjects	6 (17%)	23 (46%)	9 (41%)	3 (10%)
8 to 12				
Frequency	9.4 (7.1-11.2)	9.3 (7.6-10.7)	9.4 (7.4-10.5)	10.3 (9.1-11.5)
Amplitude	22 (6-53)	27 (16-51)	28 (14-56)	14 (6-26)
Per cent of time present	72 (7-97)	75 (19-96)	78 (26-97)	75 (7-96)
Number of subjects	35 (97%)	50 (100%)	22 (100%)	30 (100%)
12 to 18				
Frequency	14.2 (12-17)	13.3 (12-14)	Not determined	17.1 (12-20)
Amplitude	8 (6-11)	Not determined		10 (5-21)
Per cent of time present	37 (3-87)	30 (12-59)		60 (3-88)
Number of subjects	7 (19%)	6 (12%)		4 (13%)
18 to 30				
Frequency	20.7 (18-28)	20.5 (16-26)	Not determined	21.6 (19-28)
Maximum amplitude	25 (3-48)	28 (14-52)		

TABLE 2.—*Analysis of Central Electroencephalograms in Terms of Distinguishable Frequency Bands, Showing Frequency per Second, Amplitude in Microvolts, Per Cent of Time Present and Number and Per Cent of Subjects Showing More Than 5 per Cent of Each*

Frequency Bands	Normal Children No.: 36 Ages: 7-13	Behavior Problem Children No.: 50 Ages: 7-13	Constitutionally Inferior Children No.: 22 Ages: 7-13	College Students No.: 30 Ages: 18-30
2 to 5				
Frequency	4.8 (3.8-5.3)	4.5 (3.0-5.1)	4.5 (3.6-5.2)	4.7 (4.1-4.9)
Amplitude	12 (7-18)	16 (7-26)	15 (3-24)	4 (3-5)
Per cent of time	14 (5-34)	17 (5-32)	16 (5-38)	11
Number of subjects	9 (25%)	26 (52%)	5 23%)	1 (3%)
5 to 8				
Frequency	6.2 (5.3-7.6)	6.1 (5.0-7.8)	6.3 (4.9-7.6)	7.0 (5.4-8.0)
Amplitude	8 (4-13)	12 (5-21)	12 (3-26)	6 (3-15)
Per cent of time	12 (5-20)	17 (5-48)	20 (7-36)	8 (3-13)
Number of subjects	17 (47%)	41 (82%)	20 (91%)	10 (33%)
8 to 12				
Frequency	9.5 (7.6-11.5)	9.5 (7.5-11.6)	9.5 (7.8-11.0)	10.4 (9.4-12.4)
Amplitude	9 (3-16)	12 (7-17)	11 (6-20)	6 (3-13)
Per cent of time	45 (13-89)	44 (10-89)	39 (7-70)	47 (7-80)
Number of subjects	36 (100%)	46 (92%)	22 (100%)	28 (93%)
12 to 18				
Frequency	13.1 (12-16)	12.0 (10.15)	Not determined	14.3 (12-18)
Amplitude	7 (4-9)			
Per cent of time	27 (8-54)	17 (4-26)		23 (12-30)
Number of subjects	5 (14%)	5 (10%)		3 (10%)
18 to 30				
Frequency	19.8 (17-22)	21.6 (17-30)	Not determined	22.0 (18-25)
Maximum amplitude	15 (3-30)	15 (3-42)		8 (3-16)

Included under each frequency band are the averages and ranges of frequency per second, amplitude in microvolts and per cent of time the rhythm was present in the records. The number and per cent of subjects refer only to those whose records showed evidence of a particular rhythm at least 5 per cent of the time. This limit was set partly to have a uniform basis of comparison and partly to allow for errors of discrimination and measurement.

TABLE 3.—*Analysis of Frontal Electroencephalograms in Terms of Distinguishable Frequency Bands, Showing Frequency per Second, Amplitude in Microvolts, Per Cent of Time Present and Number and Per Cent of Subjects Showing More Than 5 per Cent of Each*

Frequency Bands	Normal Children No.: 36 Ages: 7-13	Behavior Problem Children No.: 50 Ages: 7-13	Constitutionally Inferior Children No.: 22 Ages: 7-13	College Students No.: 30 Ages: 18-30
2 to 5				
Frequency	4.8 (4.1-5.4)	4.4 (3.8-5.0)	4.4 (3.9-4.8)	None
Amplitude	9 (5-15)	14 (9-30)	9 (3-20)	
Per cent of time	17 (7-31)	11 (5-18)	11 (5-28)	
Number of subjects	6 (17%)	19 (38%)	3 (16%)	
5 to 8				
Frequency	6.6 (5.5-7.2)	6.3 (4.9-7.4)	6.7 (5.8-7.6)	6.8 (5.3-7.8)
Amplitude	8 (5-16)	13 (5-26)	8 (3-18)	4 (3-7)
Per cent of time	13 (5-36)	20 (5-49)	19 (5-51)	9 (3-18)
Number of subjects	9 (25%)	35 (66%)	14 (74%)	8 (27%)
8 to 12				
Frequency	9.1 (7.2-11.0)	9.3 (7.4-10.9)	9.4 (7.1-10.6)	10.3 (9.1-11.9)
Amplitude	7 (3-13)	10 (6-18)	7 (3-21)	5 (3-7)
Per cent of time	21 (5-40)	22 (5-36)	22 (5-57)	24 (12-41)
Number of subjects	31 (86%)	36 (72%)	5 (78%)	15 (50%)
12 to 18				
Frequency	14.3 (11-18)	13.9 (11-16)	Not determined	12.6 (11-14)
Amplitude	5 (3-7)			
Per cent of time	24 (12-45)	6 (5-7)		24 (23-25)
Number of subjects	6 (17%)	5 (10%)		2 (7%)
18 to 30				
Frequency	21.4 (16-26)	22.0 (17-30)	Not determined	23.0 (20-28)
Maximum amplitude	29 (7-80)	30 (7-72)		14 (8-30)

COMPARISON OF GROUPS IN TERMS OF FREQUENCY BANDS

Two to 5 per Second Rhythms.—None of the 30 college students had rhythms within this range in the occipital or frontal region, and only 1 subject's records showed such a rhythm in the central region. In all three groups of children there were some with rhythms in this frequency band, but the per cent of behavior problem children with 2 to 5 per second rhythms was approximately twice that of either the normal or the "constitutionally inferior" group. For example, in the central region (table 2) 52 per cent of the behavior problem children had 2 to 5 per second waves, whereas only 25 per cent of the normal group and 23 per cent of the "constitutionally inferior" group showed such rhythms. The average frequency of these rhythms was essentially the same in all groups, but the average measurements of amplitude and per cent of time present

were higher in the behavior problem group. Figure 1 *B* is an example of a 4 per second rhythm in the record of a behavior problem child.

Five to 8 per Second Rhythms.—The per cent of subjects with rhythms in this range was from two to three times as great in the behavior problem and "constitutionally inferior" groups as in the normal groups. The average amplitude and measurements of per cent of time present were also slightly greater in the former than in the latter groups. There were no significant differences in average frequency among the groups. Figure 1 *C* shows a prominent 6 per second rhythm in the frontal regions of a behavior problem child.

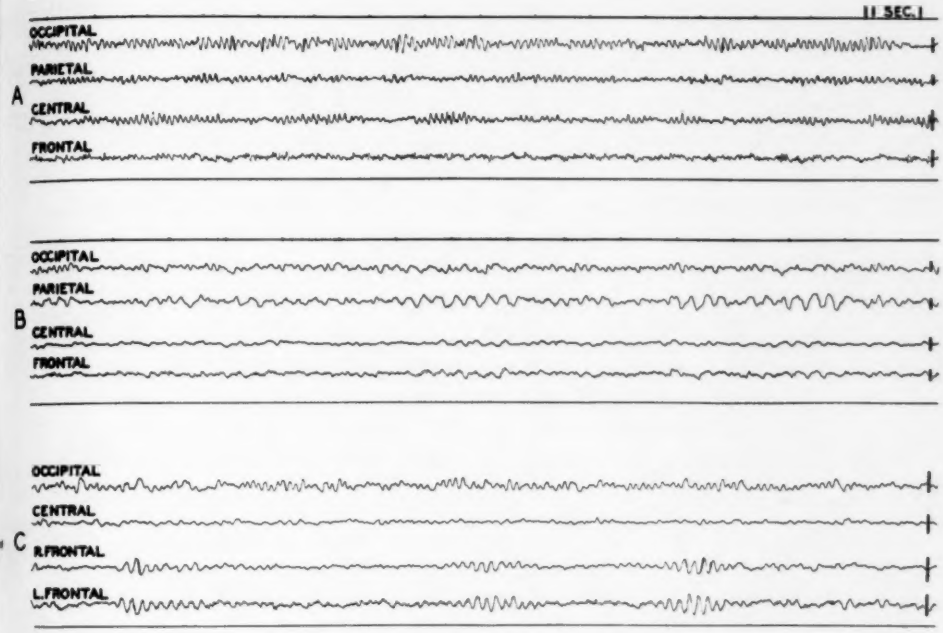

Fig. 1.—*A*, electroencephalogram of a normal 11 year old boy, showing well regulated alpha rhythms of about 10 per second in the occipital, parietal and central regions and a mixture of alpha and faster beta waves in the frontal region. *B*, electroencephalogram of an 8 year old boy with a behavior disorder, showing abnormal slow waves of 4 per second, most marked in the parietal region. *C*, record of a 10 year old boy with a behavior disorder, showing "bursts" of 6 per second waves in the frontal regions. Calibration lines equal 50 microvolts. The time line is at the top, and the signal line at the bottom, of each record.

Eight to 12 per Second Rhythms.—Among the three groups of children, all of comparable age ranges, there were no differences in the average frequency of the alpha waves, but the behavior problem and "constitutionally inferior" children had a higher average amplitude. The adult group had a higher average frequency and a lower average ampli-

tude than the younger groups, which is in agreement with results from a previous study.[2] The per cent of time measurements for all groups were similar, ranging from 72 to 78 in the occipital, 39 to 47 in the central and 21 to 24 in the frontal region.

Twelve to 18 per Second Rhythms.—Only a small per cent of subjects in any of the groups showed rhythms within this range, and, so far as can be judged from the small number of cases, there were no significant differences among the groups except that the frequency was higher in the adult group.

Eighteen to 30 per Second Rhythms.—This so-called beta band showed approximately the same average frequency and range in all the groups, but a lower maximum amplitude in the adult group.

Comment.—From the preceding analysis it is obvious that the higher frequency bands, 8 to 12, 12 to 18 and 18 to 30 per second, are of no value in differentiating the three groups of children. However, there were important differences among the groups with respect to the low frequency bands. The per cent of subjects with rhythms of 2 to 5 or 5 to 8 per second was much greater in the behavior problem and "constitutionally inferior" groups than in the normal group. The frequency of the slow waves was practically the same in all groups, but the values for amplitude and per cent of time present were in general greater in the behavior problem and "constitutionally inferior" groups. It should be emphasized that the normal adult group showed little evidence of 5 to 8 per second rhythms and almost complete absence of 2 to 5 per second rhythms. In all groups the slow rhythms when present were more frequently found in the central than in the occipital or frontal region.

FURTHER COMPARISON OF GROUPS IN TERMS OF PER CENT OF TIME MEASUREMENTS

As has been brought out by examination of the data in the tables, there are significant differences between the normal and the other two groups with respect to the per cent of subjects whose records contain more than 5 per cent of 2 to 5 or 5 to 8 per second rhythms. However, we believe that little diagnostic significance should be attached to these rhythms if present less than 10 per cent of the time. If, therefore, one accepts 10 instead of 5 per cent as the criterion of significant evidence of slow waves, the contrast between the normal and the other groups is even more impressive.

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2. Lindsley, D. B.: A Longitudinal Study of the Occipital Alpha Rhythm in Normal Children: Frequency and Amplitude Standards, J. Genetic Psychol. **55**:197-213, 1939.

This treatment of the data is shown graphically in figure 2. In the graph on the left, showing the percentages for the 2 to 5 per second waves, it may be observed that in all regions of the head the values for the behavior problem group are at least twice those for any of the other groups. Such waves are practically absent in the records of the college students and occur about equally in those of the normal and those of the "constitutionally inferior" children.

The graph on the right shows the extent to which the 5 to 8 per second rhythms are represented in the three head regions in the various groups. Again, the college students are minimally represented. The normal children are represented chiefly in the central and the frontal region, to the extent of 31 and 14 per cent, respectively. The behavior problem and the "constitutionally inferior" group, on the other hand, are alike in having from two to ten times as great a representation as the normal groups.

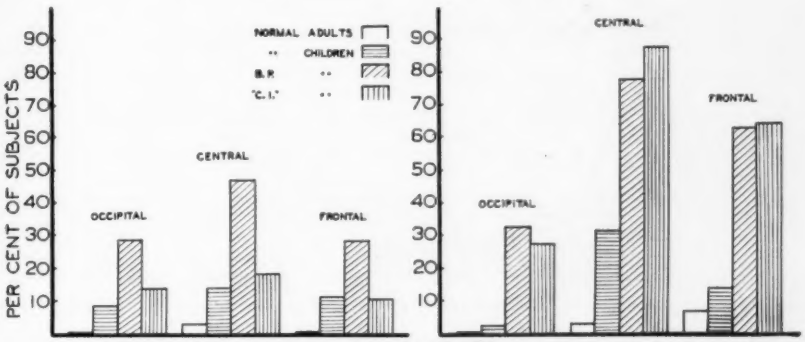

Fig. 2.—The graph at the left shows the per cent of subjects in each group with 10 per cent or more of 2 to 5 per second waves. The graph at the right shows the same for 5 to 8 per second waves.

In summary, it may be said that for any of the regions of the head less than 7 per cent of the normal adult group showed these apparently abnormal slow rhythms as much as 10 per cent of the time. Less than 15 per cent of the normal children are represented in these low frequency bands, except in the central region, where 31 per cent had 5 to 8 per second rhythms at least 10 per cent of the time. The behavior problem and "constitutionally inferior" groups form a marked contrast to the normal groups, inasmuch as they both showed a much higher per cent (80 to 90 for the central region) of subjects with 5 to 8 per second waves. Only the behavior problem group, however, showed a high per cent (46 for the central region) of subjects with 2 to 5 per second waves.

DIFFERENCES AMONG GROUPS IN RESPONSE TO HYPERVENTILATION

Another important difference between the normal groups and the behavior problem and "constitutionally inferior" groups appears to lie in the response to hyperventilation, or overbreathing. It is well known that voluntary overbreathing can be used to induce seizures in certain epileptic persons. Gibbs, Davis and Lennox [3] have shown not only that cortical signs of seizure can be produced in this way in some epileptic subjects but that, if pushed far enough, overbreathing will induce slow waves of abnormal character in normal subjects. We have found the

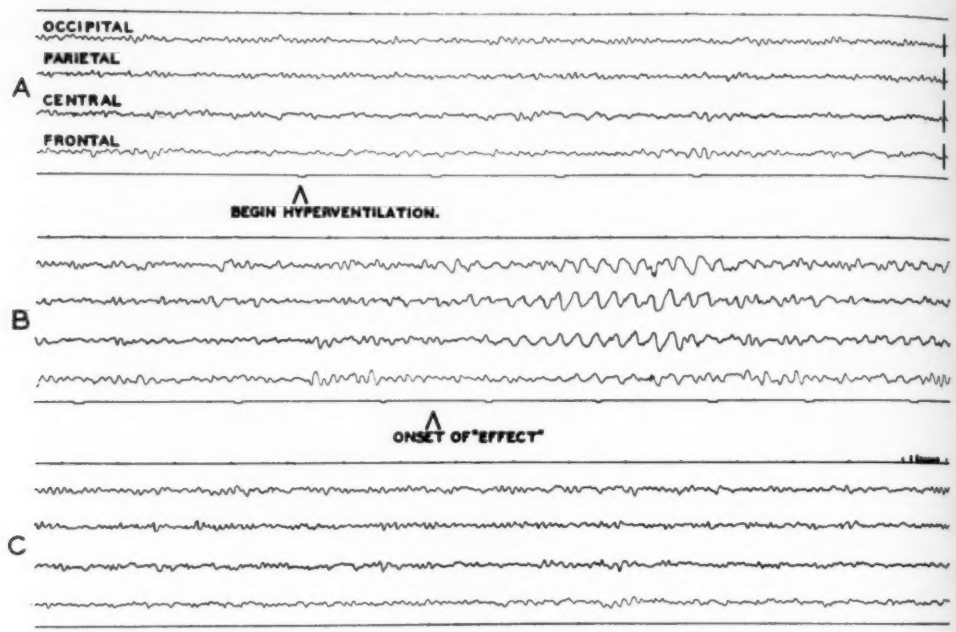

Fig. 3.—Records of an 11 year old boy with a behavior disorder, showing a "hyperventilation effect" in the form of a "burst" of 3 per second waves forty-nine seconds after the start of overbreathing. Each deep breath is indicated on the signal line. Thirty seconds of record is omitted between *A* and *B* and between *B* and *C*. *C* shows return of the electroencephalogram to the original state after hyperventilation. Calibrations equal 100 microvolts.

hyperventilation procedure valuable in bringing out latent signs of abnormality, providing it is limited to a period of about a minute to a minute and a half. To make comparisons we have determined the number of subjects in each group whose records showed within one minute after

3. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

the start of hyperventilation what we have defined as a "hyperventilation effect." Figure 3 shows such an "effect" in one of the members of the behavior problem group.

Of 42 members of the behavior problem group on whom hyperventilation procedures were carried out, 25 (60 per cent) showed a distinct "effect" similar to that seen in figure 3. Of 19 of the "constitutionally inferior" group, 9 (47 per cent) were found to give a "hyperventilation effect." In contrast to the results in these two groups, only 7 (21 per cent) of the 34 normal children and only 1 (6 per cent) of the 17 normal adults on whom this procedure was carried out gave a "hyperventilation effect." Not only did smaller percentages of normal subjects give a "hyperventilation effect" but the "effect" was less marked in suddenness of onset, amplitude and persistence of the slow waves than in the other groups.

The onset of the "effect" was earlier in the behavior problem group than in any of the other groups. When "hyperventilation effects" occurring within ninety seconds are considered, the average duration of hyperventilation until the onset of an "effect" was thirty-two seconds in the behavior problem group, thirty-nine seconds in the "constitutionally inferior" group and fifty seconds in the group of normal children. It was found also that the slow waves induced persisted longer after cessation of hyperventilation in the behavior problem group (average duration, twenty-six seconds) than in the "constitutionally inferior" group (ten seconds) or in the normal group (fourteen seconds).

QUALITATIVE DIFFERENCES IN PATTERNS OF ACTIVITY

The measurements of frequency, amplitude and per cent of time of the various rhythms characterize the patterns of activity in the electroencephalogram to a certain extent, but there are some aspects of the patterns which are not readily quantified, namely, the regularity in the shape and duration of successive waves, the sharp or slow modulations of amplitude and the irregular fluctuations from one pattern to another. We believe that the patterns of activity found in records of behavior problem children, particularly in the central and frontal regions, tend to be more disorganized (irregular in shape and rhythm) than those of normal subjects. However, when slow waves are present they are often more rhythmic and regular in the behavior problem group than in the normal subjects. The slow waves, owing partly to the slight increase in size and per cent of time present in the records of behavior problem children, but also to their organized appearance in "bursts" or series," stand out more clearly than do those found in the tracings of normal subjects.

COMMENT

Analysis of the electroencephalograms has revealed three main factors which distinguish the behavior problem children as a group from the group of normal children. These factors are a higher per cent with 2 to 5 per second waves, 5 to 8 per second waves and "hyperventilation effects" among the members of the behavior problem group. With respect to the 2 to 5 per second waves the "constitutionally inferior" children were more like the normal children, but with respect to the 5 to 8 per second waves they were more like the behavior problem children. A highly selected group of normal adults (college students) showed little evidence of either type of rhythm.

Slow waves of 2 to 5 per second in a waking subject are generally conceded to be abnormal, and their absence in the majority of the normal children and adults in our series supports this contention. Waves of this frequency are thought to be associated particularly with convulsive-like disturbances, and although the 2 to 5 per second waves found (in the central region) in about 45 per cent of our behavior problem subjects were of smaller magnitude than, and often of different pattern from, those associated with actual seizures, we believe that they are an indication of convulsive tendencies. None of the behavior problem children included in this study had a clinical history of seizures of any kind, but it is thought that the 2 to 5 per second waves in their records may be suggestive of subthreshold convulsive activity.

Waves of 5 to 8 per second frequency are also thought to be abnormal in waking states, and Gibbs, Gibbs and Lennox [4] associated certain patterns of waves within this frequency range with psychomotor epilepsy. The majority of the normal children and adults in our series did not show waves of 5 to 8 per second in significant amounts, although as many as half of the normal children and 30 per cent of the college students had them at least 5 per cent of the time in the central region. On the other hand, only 1 of the college students and only 31 per cent of the normal children had as much as 10 per cent of the 5 to 8 per second waves in the central region, whereas from 80 to 90 per cent of the behavior problem and "constitutionally inferior" children had such rhythms.

Apparently, then, occasional very brief runs of 5 to 8 per second waves in the frontal and central regions are not unusual in normal subjects, but it is our belief that if they are present as much as 10 per cent of the time in well organized "runs" or "bursts" they should be

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937; The Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy, Am. J. Psychiat. **95**: 255-269, 1938.

considered abnormal. On this basis the majority of the behavior problem and "constitutionally inferior" children in our series showed rhythms which come under the abnormal classification, whereas few of the normal children and none of the normal adults had rhythms which would be so classified.

Not only were the slow waves which we have interpreted as abnormalities or cortical disturbances more frequently found in the records of the behavior problem and "constitutionally inferior" groups, but the "hyperventilation effects," which we interpret as latent signs of abnormality, were present to a more marked degree and in a larger per cent of cases than in the normal groups. Also, the "hyperventilation effects" appeared earlier and persisted longer in the behavior problem group than in the other groups. These facts suggest that the behavior problem children had a lower cortical threshold of excitation and a greater sensitivity to all sorts of disturbances arising in the cortex.

This might be interpreted to mean that minor lesions, atrophy, irritations and the like, although insufficient to produce neurologic symptoms, could in some way serve to excite a sensitive cortex and thus produce the slow rhythms. We are more inclined to believe, however, that the slow rhythms are in large part due to some underlying physiologic imbalance, such as shifts in the acid-base balance or the blood sugar level or disturbances in equilibrium of other constituents of body fluids. The influence of hyperventilation in accentuating slow rhythms already present, and in some cases in introducing new ones, seems to support this notion. Hyperventilation by increasing the p_H of the blood apparently lowers the excitatory threshold of the cortex and favors the development of slow waves of increased magnitude.

Whatever the cause, the greater prevalence of the two types of slow waves and "hyperventilation effects" in the behavior problem children than in the normal children suggests a disturbance of cortical function which may be an important factor in the inability of the former group to adjust to environmental conditions, particularly if such conditions are adverse. On the same basis, one might expect that the so-called normal children whose electroencephalograms showed significant evidence of disturbances in the form of slow waves would be poorer risks in the face of persistent environmental difficulties than those whose records did not show such electrocortical disturbances. Of the "constitutionally inferior" group, who showed as high a percentage of subjects with 5 to 8 per second waves as the behavior problem group, 5 presented definite behavior problems according to reports from housemothers, even though they lived in a protected and restricted institutional environment. The others of the group presumably would not do well except under the most favorable environmental circumstances, or under rigid control in an institutional environment.

In a subsequent paper dealing only with behavior problem children an attempt will be made to classify their electroencephalograms still further and to relate them to the various types of behavior observed as well as to other possible factors involved.

SUMMARY

A detailed analysis of the electroencephalograms from the occipital, central and frontal regions of the head is presented for four groups of subjects: 30 normal adults, 36 normal children, 50 behavior problem children and 22 "constitutionally inferior" children. The analysis is in terms of the frequency, amplitude and per cent of time of the rhythms grouped according to frequency bands.

The electroencephalograms of the behavior problem children differ from those of the normal children in three main ways, by showing a higher per cent of subjects with (1) 2 to 5 per second waves, (2) 5 to 8 per second waves and (3) abnormal activity induced by hyperventilation. In addition, the average per cent of time present and the amplitude of the slow waves are greater for the behavior problem group than they are for the small group of normal subjects with such rhythms. The "constitutionally inferior" group resembles the behavior problem group, but has a lower per cent of subjects with 2 to 5 per second waves. The frequency bands above 8 per second are of no value in differentiating the three groups of children. There is little evidence of either type of slow waves or of response to hyperventilation in the normal adult group.

The differences in the amount of abnormal slow waves among the various groups are discussed and the suggestion is made that such disturbances of cortical function are probably important factors in the causation of behavior disorders.

CEREBRAL METABOLISM IN MONGOLIAN IDIOCY AND PHENYLPYRUVIC OLIGOPHRENIA

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For any organ to function properly a constant supply of energy must be available. This energy is obtained from the oxidation of various foodstuffs. The brain oxidizes sugar predominantly. For this reason cerebral disturbances may develop as results either of hypoglycemia or of anoxia. The brain is more sensitive than other organs to lack of oxygen. If the cerebral circulation is interrupted for a few seconds unconsciousness supervenes. Similarly, hypoglycemia may produce impairment of the functions of the brain. The brain is unlike other organs, which seem to oxidize both fat and carbohydrate. For example, the oxygen uptake of muscle remains unchanged during hypoglycemia, as muscle can oxidize fat when carbohydrate is not available.[1] The brain, on the other hand, when deprived of its chief foodstuff is no longer able to sustain its functions, so that coma may develop. A cerebral respiratory quotient close to unity, a value which indicates the oxidation of carbohydrate, has been observed in animals [2] and in human subjects.[3]

Thus, the utilization of oxygen and sugar affords a measure of cerebral metabolism. Preliminary observations indicate that the consumption of oxygen per hundred cubic centimeters of blood traversing the adult human brain is 7.43 volumes per cent, while that of sugar is about 14.6 mg. per hundred cubic centimeters. The purpose of the present investigation is to study the metabolism of the brain in cases of mongolian idiocy and phenylpyruvic oligophrenia. Mongolian idiocy is a name given to a type of mental deficiency associated with special physical peculiarities (the patients were selected by Drs. Humphreys and Kreezer [3a] according to the specifications of Drs. Doll and Kuenzel).

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1. Himwich, H. E., and Fazekas, J. F.: Endocrinology **21**:800, 1937.

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3a. Kreezer, G.: Am. J. Psychol. **52**:503, 1939.

A rarer type of mental deficiency has been termed phenylpyruvic oligophrenia by Jervis.[4] The members of this group usually are more retarded mentally than the mongolian idiots and possess different physical features. They eliminate an abnormal substance in the urine, phenylpyruvic acid. The number of persons with phenylpyruvic oligophrenia, though smaller than that of mongoloid idiots, included, nevertheless, all that were available in such a large institution as Letchworth Village.

METHOD

Samples of arterial and of venous blood were collected practically simultaneously. The arterial blood was drawn usually from the femoral artery and occasionally from the brachial or the internal carotid artery. The venous blood was obtained from the internal jugular vein, just as it leaves the cranium at the jugular foramen, by the method of Myerson, Halloran and Hirsch.[5] In infants a third sample of blood was taken from the longitudinal sinus, through the patent fontanel. These samples of blood were analyzed for their oxygen [6] and sugar [7] contents. The difference between the oxygen and sugar contents of the arterial and those of the venous blood revealed the cerebral utilization of these substances. Peripheral circulation time was also determined by the objective method of Robb and Weiss,[8] in order to obtain data on the circulation rate of the subjects.

RESULTS

The accompanying table presents the results obtained in 65 persons with mongolism. The cerebral oxygen utilization of 45 adults with mongolism was 5.62 volumes per cent. This value is significantly less (1.81 ± 0.17) than the average of 7.43 volumes per cent for normal persons. The difference of 1.81 volumes per cent reveals a reduction of 24.4 per cent. The sugar uptake was also decreased and averaged 7 mg. per hundred cubic centimeters, in contrast to 14.6 mg. per hundred cubic centimeters for the controls. The circulation time obtained for 33 adults with mongolism averaged twelve and seven-tenths seconds, as against fifteen and six-tenths seconds for the controls. The average oxygen consumption of the children with mongolism of 4.98 volumes per cent appears more depressed than that of the adults, but $P = 0.15$

4. Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of Fifty Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid, Arch. Neurol. & Psychiat. **38**:944 (Nov.) 1937.

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7. Hagedorn, H. C., and Jensen, B. N.: Biochem. Ztschr. **135**:46, 1923.

8. Robb, G. P., and Weiss, S.: Am. Heart J. **8**:650, 1932.

by Fisher's method, which shows that the difference cannot be regarded as statistically significant. The six observations made on infants with mongolism by comparison of samples of the arterial and of the internal jugular venous blood yielded the lowest average, 3.72 volumes per cent. This value, with $P < 0.01$, is significantly less than that of the adults with mongolism. In addition, blood was drawn from the fontanel on four occasions, and the average uptake was found to be 3.63 volumes per cent. This is in contrast to the value for the normal infants, who had an average of 8.59 volumes per cent. The difference is 4.76 volumes per cent, a reduction of 57.7 per cent. The oxygen content of the cerebral blood, which was lowest in the infants, 14.51 volumes per cent, increased to 15.71 volumes per cent in the children and attained a value within normal limits, 18.49 volumes per cent, in the adults.

Fifteen persons with phenylpyruvic oligophrenia (whose ages ranged from 5 to 39 years, with an average of 20 years) had an average oxygen

Observations on Persons with Mongolian Idiocy and Phenylpyruvic Oligophrenia

Condition	Number of Observations	Average Arteriovenous Difference in	
		Oxygen, Vol. %	Sugar, Mg. per 100 Cc.
Mongolism			
Adult	45	5.62	7
Children	14	4.98	
Infants (internal jugular vein)	6	3.72	
Infants (fontanel)	4	3.63	
Phenylpyruvic oligophrenia	14	5.84	8

consumption of 5.84 volumes per cent, a decrease of 1.59 volumes per cent, or 21.4 per cent, below that of the controls. This difference may be regarded as significant, for $P = 0.01$. The sugar uptake in cases of phenylpyruvic oligophrenia was reduced to 8 mg. per hundred cubic centimeters. The average oxygen content of the arterial blood was 16.74 volumes per cent.

COMMENT

Mongolism.—A review of the results obtained in mongolian idiots reveals a diminished utilization of oxygen and sugar from each hundred cubic centimeters of blood passing through the brain. This may be caused either by decreased cerebral metabolism or by a faster blood flow or by both. It is true that one does not know the rate of cerebral blood flow, but if in the resting subject it is proportional to that of the systemic circulation, then it is not very different from the normal, for the circulation time of the subjects with mongolism, twelve and seven-tenths seconds, is approximately that of the controls, fifteen and six-tenths seconds. The difference, if significant, may be imputed to

the shorter distance traversed by the injected cyanide, as a result of the smaller stature of the persons with mongolism.

In an effort to evaluate the two possible factors of increased blood flow and diminished cerebral metabolism, it is of aid to use data obtained by methods other than those employed in this study. Meyer and Jones [9] came to the conclusion that the brains of some persons with mongolism reveal changes similar to those found in carbon monoxide poisoning. In both instances proliferation of the fibrous glia are interpreted as secondary to anoxia. Thus, it would seem that the cerebral tissues of persons with mongolism suffer from anoxia because they are incapable of utilizing the oxygen present in the blood. With the pulmonary and circulatory apparatus functioning normally in these persons, the arterial blood carried a volume of oxygen which was somewhat reduced but was, nevertheless, adequate for the cerebral requirement. If a decrease of metabolism exists, it cannot be imputed to impairment of the oxygen supplies but must be ascribed to changes in the cerebral structure or function. Endocrine changes are characteristic of mongolism,[10] and since the internal secretions influence the rate of enzymatic reactions, the decrease of cerebral metabolism in mongolism may be caused by impairment of one or another of the enzyme systems which facilitate oxidations.

Phenylpyruvic Oligophrenia.—The patients with phenylpyruvic oligophrenia, like those with mongolism, also exhibited decreased utilization of oxygen and sugar per hundred cubic centimeters of blood. The data on these subjects are not as numerous as those obtained for the patients with mongolism, but nevertheless are sufficient to reveal a decreased arteriovenous difference in oxygen content of cerebral blood. If this is an indication of diminished cerebral metabolism, such a diminution may be imputed to lack of an oxidative enzyme, a defect similar to that which prevents the oxidation of phenylalanine. Recent work reveals that normal babies born prematurely exhibit a similar defect in the metabolism of phenylalanine and tyrosine.[11] In the premature infants, however, this condition may be remedied by the administration of increased amounts of vitamin C, a substance which probably acts catalytically, like an enzyme.

Relation Between Mental Deficiency and Reduced Cerebral Metabolism.—Experimental work has revealed that diminished cerebral

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10. Benda, C. E.: Studies in Mongolism: II. The Thyroid Gland, Arch. Neurol. & Psychiat. **41**:243 (Feb.) 1939; III. The Pituitary Body, ibid. **42**:1 (July) 1939.

11. Levine, S. Z.; Marples, E., and Gordon, H. H.: Science **90**:620, 1939.

metabolism, whether due to lack of oxygen [12] or of sugar,[13] may lead to permanent changes in cerebral function, changes which persist after the sugar and oxygen again become available to the brain. With an inadequate cerebral metabolism in early life the brain may never gain normal function. In this connection it is especially significant that the younger the person with mongolism, the greater the decrease in cerebral metabolism. The energy supplies are inhibited most profoundly just at the time that growth is greatest and therefore most damage can be done by inadequate metabolism. This is in agreement with morphologic studies which have revealed [14] that the brain as a whole, especially the brain stem and the cerebellum, exhibit lack of development. If this explanation is correct, the mechanism of the mental deficiency may be compared with the changes produced in the experiments of Andreyev,[15] who produced depressed cerebral metabolism by ligating cerebral blood vessels in a dog 1½ months old. At the age of 2 years the behavior of this animal remained that of a puppy. Similarly, in phenylypruvic oligophrenia, the mental deficiency may be secondary to the impairment of cerebral metabolism. At present, however, the available data are insufficient to establish the mechanisms for the production of mental deficiency, which may be different in mongolism and in phenylpyruvic oligophrenia. There are three possible relationships between mental deficiency and depressed cerebral metabolism. The mental deficiency may be the result of diminished cerebral metabolism and associated structural changes starting during early development. It is also possible that the deficiency and the impairment of cerebral oxidation are independent products of the same underlying cause, for example, an enzyme deficiency. Finally, the depression of cerebral metabolism and the mental deficiency may be unrelated phenomena. Changes have been observed by Kreezer [3a] in electroencephalograms of persons with mongolism. But there are no data indicating the relationship between these changes and metabolic processes.

Both in mongolian idiocy and in phenylpyruvic oligophrenia, oxygen and sugar are consumed in stoicheometric proportions, approximately 3 cc. of oxygen to 4 mg. of sugar. It is interesting that in normal subjects more sugar disappears than can be accounted for by utilization

12. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

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14. Davidoff, L. M.: The Brain in Mongolian Idiocy: A Report of Ten Cases, Arch. Neurol. & Psychiat. **20**:1229 (Dec.) 1928.

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of oxygen. A similar phenomenon occurs in persons with schizophrenia.[16] In the two mental deficiencies under consideration, however, the theoretic stoicheometric relationship has been found. An explanation of this difference is not available.

The oxygen content of the arterial blood in infants with mongolism is low, indicating anemia. This adds to their difficulties of survival. However, as in the case of oxygen uptake, the condition improves with age. The average arterial oxygen content for the patients with phenylpyruvic oligophrenia is also low.

CONCLUSION

In mongolian idiocy the brain removes less than the normal amount of oxygen and sugar from each hundred cubic centimeters of blood passing through that organ. The same phenomenon, though to a lesser extent, is observed in phenylpyruvic oligophrenia. Such results might be caused by a decrease in cerebral metabolism or by a faster cerebral blood flow. A review of the literature indicates that the diminished metabolism of the brain is the more probable of the two alternatives. Possible relationships between mental deficiency and diminished cerebral metabolism are discussed.

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PALLIDOHYPOTHALAMIC TRACT, OR X BUNDLE OF MEYNERT, IN THE RHESUS MONKEY

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The term pallidohypothalamic tract was used by Bard and Rioch (1937) [1] to designate a bundle of well myelinated fibers which they observed leaving the main bundle of pallidofugal fibers and running into the hypothalamus, to end, or at least to lose their myelin sheaths, in the region of the ventromedial hypothalamic nucleus. These observations were made on a decorticate cat from which the corpus striatum had not been removed. The origin from the corpus striatum of the bundle in question was shown by its degeneration in another decorticate cat, in which the corpus striatum was destroyed along with the cortex. Various terms have been applied to this bundle, and it will serve to avoid confusion if the synonyms are listed here.

The pallidohypothalamic tract has been described under that name by Papez,[2] and by Ranson and Ranson [3]; and as the hypothalamic fasciculus by Krieg [4]; hypothalamic tegmental tract by Rioch [5]; *pinselförmiges Faserbündel* by Kodama [6]; decussatio anterior regionis subthalamicae by Ganser [7]; fasciculus of the tuber cinereum by von Gudden,[8]

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Déjerine,[9] Nicolesco and Nicolesco[10] and Tilney and Riley,[11] and *X Bündel* by Meynert,[12] Forel,[13] Schnopfhagen[14] and von Kölliker.[15] As some of these terms indicate, the pallidohypothalamic tract has often been confused with Ganser's commissure, because the fibers of the two overlap to some extent.

This relation is well illustrated by figures 2 and 3 accompanying the paper by Ranson and Ranson.[3] The most rostral fibers of the pallidohypothalamic tract intermingle with those of Ganser's commissure, but the majority of the fibers lie in a plane caudal to that occupied by the commissural fibers.

There have been available for study sections of the brain of 2 rhesus monkeys (Macaca mulatta), which as a result of degenerations produced by fortunately situated lesions, placed with the Horsley-Clarke instrument, have shown clearly that the pallidohypothalamic tract and Ganser's commissure are separate and distinct. Frontal sections of the brain of monkey 14, stained alternately by the Weil and the cresyl violet method, revealed a lesion in the anterior part of the hypothalamus to the left of the midline, extending ventrad as far as the optic chiasm. The lesion resulted in bilateral degeneration (wallerian and retrograde) of the commissure of Ganser, but Meynert's commissure was not seriously damaged (fig. 1 *A*, at *M*). At a slightly more caudal level the lesion destroyed the pallidofugal fibers and the fornix, but on the opposite side the ansa and the fasciculus lenticularis were seen to be intact, and from the caudally directed pallidofugal bundle, formed by the union of the ansa and the fasciculus lenticularis, a pencil-like bundle was directed ventromedially toward the ventromedial hypothalamic nucleus (fig. 1 *B*). This was the pallidohypothalamic tract, and it remained unchanged, although Ganser's commissure was degenerated.

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9. Déjerine, J.: Anatomie des centres nerveux, Paris, Rueff & Cie, 1895, vol. 1; 1901, vol. 2.

10. Nicolesco, I., and Nicolesco, M.: Quelques données sur les centres végétatifs de la région infundibulotubérienne et de la frontière diencéphalo-télencéphalique, Rev. neurol. **2**:289, 1929.

11. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 3, New York, Paul B. Hoeber, Inc., 1938.

12. Meynert, T.: The Brain of Mammals, in Stricker, S.: Manual of Histology, translated by H. Power, J. J. Putnam, J. O. Green and others, New York, William Wood & Company, 1872, chap. 32, p. 650.

13. Forel, A.: Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehrin des Menschen und einiger Säugethiere, mit Beiträgen zu den Methoden der Gehirnuntersuchung, Arch. f. Psychiat. **7**:393, 1877.

14. Schnopfhagen, F.: Beiträge zur Anatomie des Sehhügels und dessen nächster Umgebung, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **76**:315, 1877.

15. von Kölliker, A.: Handbuch der Gewebelehre des Menschen, ed. 6, Leipzig, Wilhelm Engelmann, 1896.

Ganser's commissure had not entirely disappeared. On the side opposite the lesion, some of the fibers were seen to persist dorsal to Meynert's commissure in a fragmented and degenerating condition (fig. 1 *A*, at *G*). At the level of the anterior pillar of the fornix some

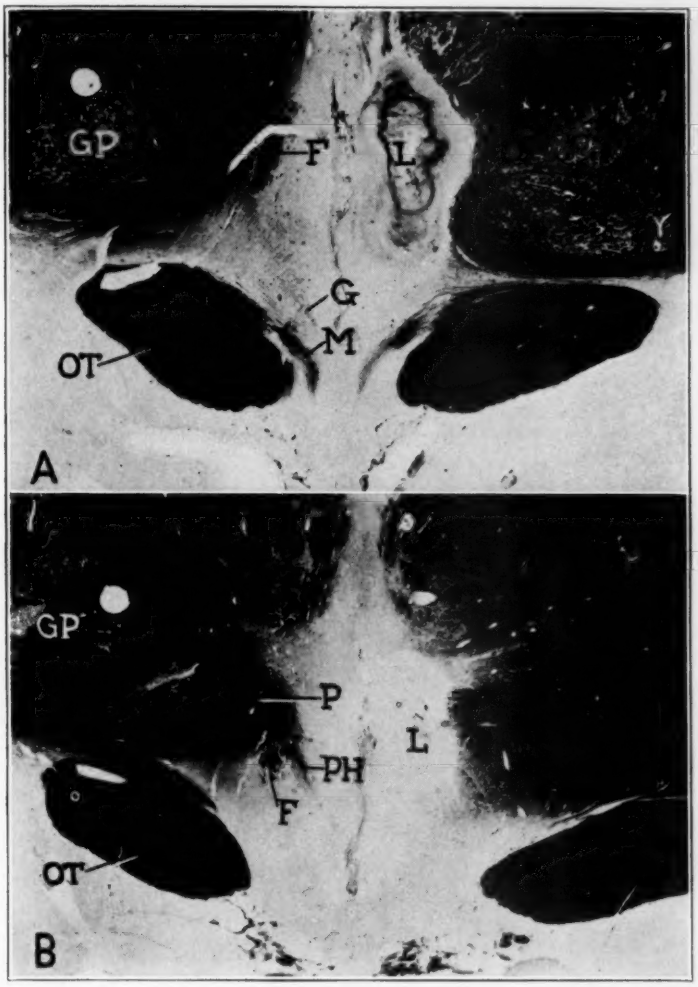

Fig. 1.—Photomicrographs from frontal sections of the brain of monkey 14 (stained by Weil's method), showing the intact pallidohypothalamic tract and the degenerated Ganser's commissure. In this figure and in figure 2, *F* indicates the fornix; *G*, Ganser's commissure; *G P*, the globus pallidus; *L*, the lesion; *M*, Meynert's commissure; *O T*, the optic tract; *P*, the pallidofugal bundle, formed by the junction of the ansa and the fasciculus lenticularis, and *P H*, the pallidohypothalamic tract.

of these degenerating fibers could be traced toward the fornix, but few passed through it. On the other hand, the normal fibers of the pallidohypothalamic tract, running at right angles to the fornix, passed for the most part across its medial border, although a considerable number ran

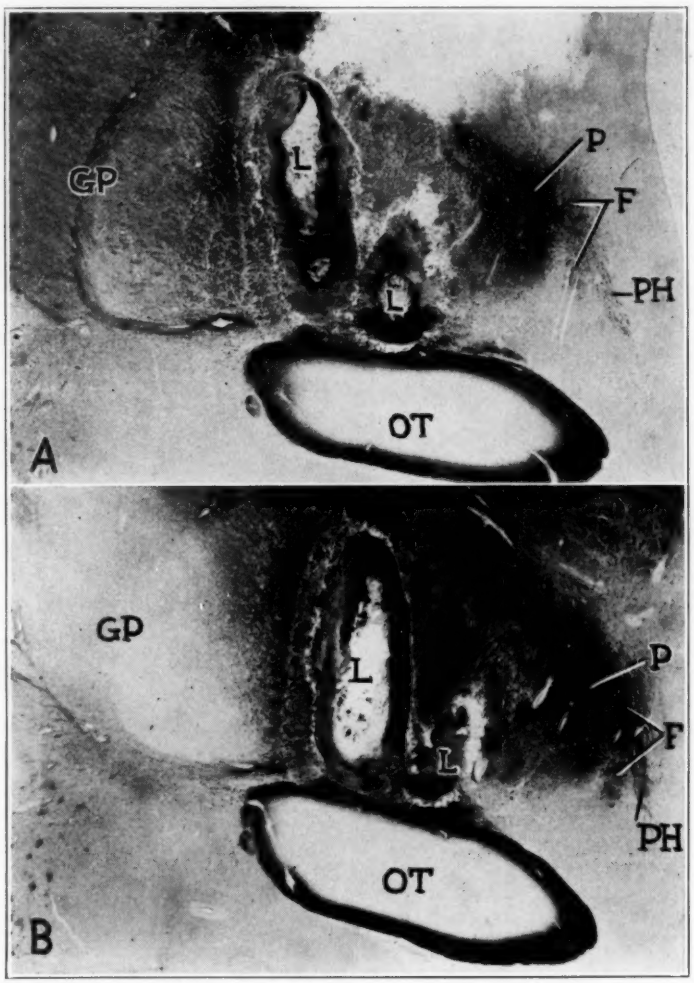

Fig. 2.—Photomicrographs from frontal sections of the brain of monkey S6 (stained by the Marchi method), showing degeneration of the pallidohypothalamic tract resulting from damage to the globus pallidus.

directly through it. The absence of degeneration in the pallidohypothalamic tract shows that it is independent of Ganser's commissure.

The brain of monkey S6, which had been prepared by the Marchi method and cut in frontal sections, had a lesion in the medial part of

the globus pallidus and zona incerta on the right side. The ansa and fasciculus lenticularis were degenerated, the two forming a large bundle of degenerated fibers which coursed caudad along the medial border of the globus pallidus. The degenerated pallidohypothalamic tract could be seen emerging from this pallidofugal bundle, running ventromedially into the hypothalamus and passing either directly through the fornix (fig. 2*A*) or medial to it (fig. 2*B*). It is clear that these fibers came from the globus pallidus. There were no degenerated fibers of the same caliber to be seen in the zona incerta. The origin of the fibers in the globus pallidus is thus confirmed.

PARTIAL THENAR ATROPHY

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AND
MAX MICHAEL JR., M.D.
BOSTON

Recently, Wartenberg described a clinical entity which he called partial thenar atrophy.[1] He reviewed the literature and presented 7 new cases. These cases were characterized by the slow development of partial atrophy, limited to the muscles on the radial side of the thenar eminence and involving only the abductor pollicis brevis and the opponens pollicis muscle. Four of the 7 patients had bilateral atrophy. No other appreciable objective signs were noted, but most patients complained of paresthesias in the fingers of long duration. There was no history of trauma or of significant toxic factors in the cases presented by him.

The 3 cases which we report differ from those previously published in that objective sensory and vasomotor disturbances could be demonstrated and that partial thenar atrophy with sensory and vasomotor changes occurred in 1 case after trauma to the median nerve. The second case is presented to show the similarity in the atrophy in cases of known lesions of the median nerve to that found in cases in which no such lesion exists.

The condition is benign and is of practical significance, as it may be confused with progressive disabling diseases, such as progressive muscular atrophy, amyotrophic lateral sclerosis, syringomyelia and tumor of the spinal cord.

REPORT OF CASES

CASE 1.—C. S., a housewife aged 50, with inactive tuberculosis of the right hip joint and rheumatoid arthritis of the fifth and sixth cervical vertebrae, had experienced pains in the joints, stiffness and hot flashes ten years before entrance to the hospital. There was excruciating pain along the entire left arm and in the left shoulder for four months, after which she noted parasthesias in the finger tips of the left hand, blanching in this area and atrophy of part of the left thenar eminence. The atrophy has remained stationary. Paresthesias and blanching have persisted. In addition, she has had occasional paresthesias in the fingers of the right hand and the toes of both feet. There was no history of intoxication or of special occupational use of the hands.

From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

1. Wartenberg, R.: Partial Thenar Atrophy, Arch. Neurol. & Psychiat. **42**:373 (Sept.) 1939.

Examination.—The extremities showed the following changes: The extreme tips of the thumb and second and third fingers of the left hand were blanched, and the skin over these areas was tough, dry and fissured. There was some diminution in the ability to abduct, rotate and oppose the left thumb; all other movements

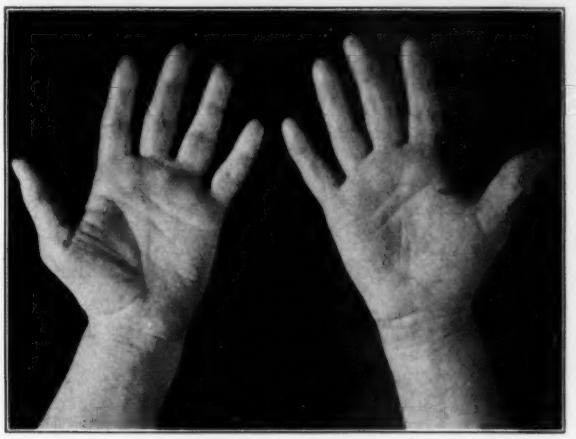

Fig. 1.—Left partial thenar atrophy in case 1.

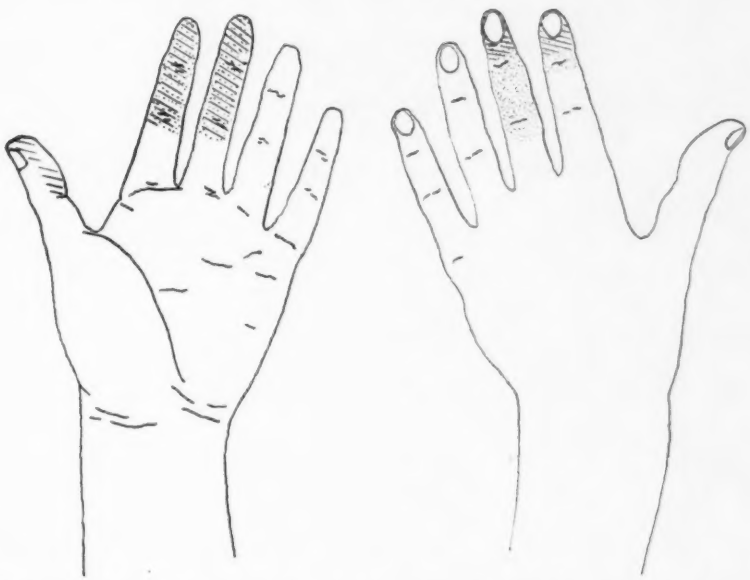

Fig. 2.—Hypesthesia to touch and pain (cross hatching) and loss of sweating (dotted areas) in case 1.

of the left hand were within normal limits. There was demonstrable atrophy on the radial side of the left thenar eminence (fig. 1). Sensory examination revealed hypesthesia to touch and pinprick along the palmar surfaces of the distal two phalanges of the index and middle fingers and the dorsal surface of the distal

phalanx of the index and the middle finger (fig. 2). The patient's legs were placed in hot water for thirty minutes, until profuse sweating was produced. The extent of the sweating was observed in the hands, which had been prepared

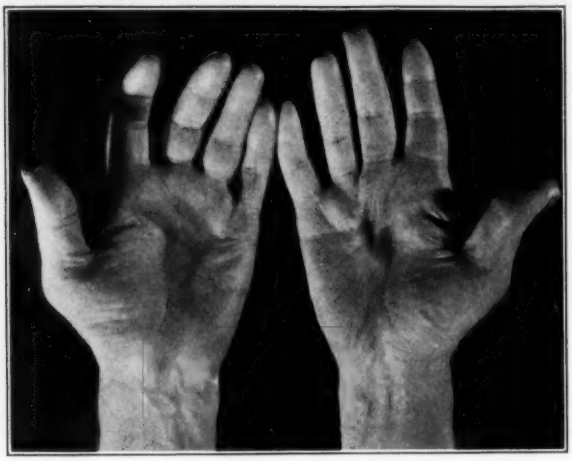

Fig. 3.—Left partial thenar atrophy in case 2.

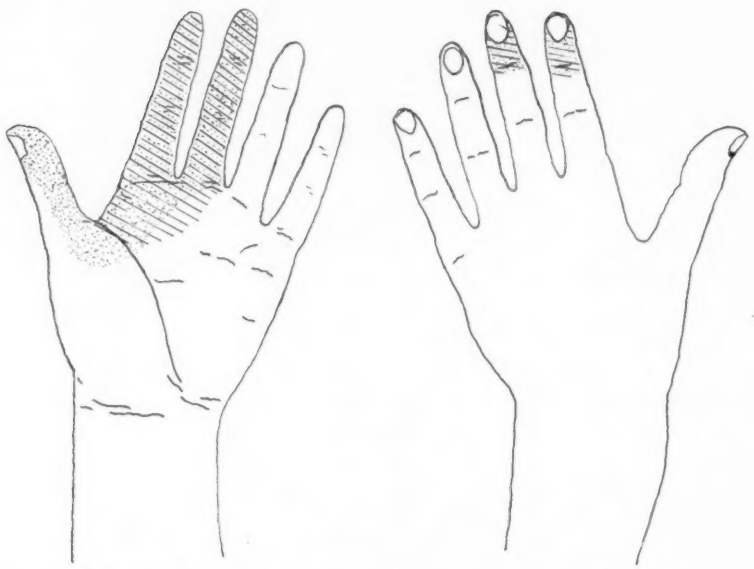

Fig. 4.—Hypesthesia to pain and touch (cross hatching) and loss of sweating (dotted areas) in case 2.

with iodine and starch. There was no sweating over the palmar hypesthetic area of the index and middle fingers. Dorsally, no sweating was observed on the distal two phalanges of the middle finger and the distal phalanx of the index finger (fig. 2). Roentgen examination showed no evidence of cervical rib but there

was hypertrophic arthritis between the fifth and the sixth cervical vertebra. Roentgenograms of the hands showed the bones to be slightly atrophic, especially about the joints.

Fig. 5.—Left partial thenar atrophy in case 3.

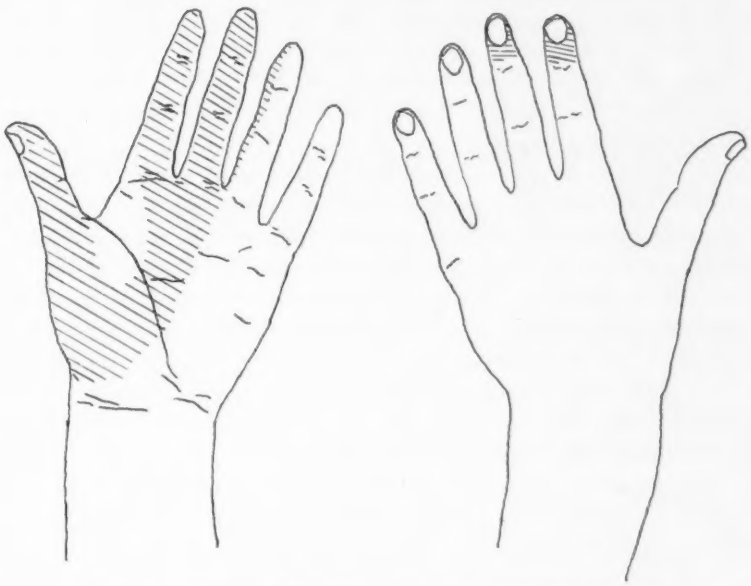

Fig. 6.—Hypesthesia to touch and pain (cross hatching).

CASE 2.—H. F. M. a married, unemployed salesman aged 55 gave a history of psychomotor and grand mal epilepsy for the past sixteen years. Fifteen years ago he had lacerated the left forearm along the flexor surface of the lower third. Eleven days later he had no motor disability of the hand, but complained of sharp, constant pain in the left index finger, extending down to the thenar eminence, where it was most intense. Examination revealed anesthesia to pinprick along

the left index finger, extending down to the thenar eminence, and the palmar aspect of the distal half of the thumb. Two years later it was noted that he had anesthesia of the index finger and most of the middle finger of the left hand. Motor function was unimpaired, and no atrophy was noted. The patient stated that he had noted a groove along the thenar eminence two years before.

Examination.—There was atrophy along the radial aspect of the left thenar eminence (fig. 3). Slight weakness appeared in abduction and rotation of the thumb. Other movements of the hand were well within normal limits. There was hypesthesia to pinprick and touch on the palmar surfaces of the index and middle fingers distal to the thenar eminence, and on the dorsal surfaces of the distal phalanges of these fingers (fig. 4). Loss of sweating was observed in the hypesthetic area and along the palmar surface of the distal half of the thumb (fig. 4).

CASE 3.—I. W., a West Indian Negress aged 68 with hypertensive cardiovascular disease, was found to have partial thenar atrophy along the radial border of the left hand (fig. 5). She had been unaware of the atrophy. She had complained of tingling of all the fingers for a number of years. There was no history of intoxication, infection or special occupational use of the hands. Abduction and opposition of the thumb were weak. There was hypesthesia to pinprick and touch on the palmar surfaces of the index and middle fingers, which extended in an incomplete fashion over the thenar eminence. The dorsal aspects of the distal phalanges of the index and middle fingers were insensitive to these stimuli (fig. 6). With one test, it was not possible to demonstrate any disturbance of sweating in the hands. No fibrillations or other neurologic findings were noted except for a parkinsonian tremor of the hands and fingers on both sides.

COMMENT

Wartenberg offered two explanations for partial thenar atrophy. The first was based on "toxicotraumatic" damage of the corresponding branches of the median nerve. He expressed the belief that the paresthesias were an expression of chronic sensory polyneuritis resulting from undetermined toxic processes. He asserted that in some persons the traumatic factor was due to the course of these branches of the median nerve in their relation to the ligamentum carpi transversum. He suggested that these branches may be subjected to abnormal pressure, stretching or strangulation in the ordinary use of the hand. He explained the rarity of the condition by the fact that these two factors need to be combined to produce the partial thenar atrophy.

His second explanation, which seemed more convincing to him, is based on the assumption that there is an abiotrophy of the phylogenetically youngest muscles in the thenar eminence, which may be precipitated by added external damage.

In our second case, partial thenar atrophy with objective sensory and vasomotor changes were observed after trauma to the forearm in the region of the median nerve. There is little doubt that the trauma to the nerve was a causal factor in the muscular atrophy. It is known that in the early stages of injury to the median nerve marked flattening of the

outer part of the thenar eminence occurs. Of the small muscles of the hand, the opponens pollicis is the last to recover.[2]

It is conceivable that in our first case the original pain in the arm and shoulder represented diffuse involvement of the brachial plexus, either by nonspecific neuritis or by arthritis of the cervical vertebrae, which has been demonstrated. Atrophy then occurred only in certain muscles of the thenar eminence. Here, too, sensory and vasomotor changes remained impaired. At present there is no evidence that the patient has uniradicular brachial palsy,[3] as the lesion is too discrete.

Our third case corresponds in all respects to those described by Wartenberg except for the objective sensory changes.

It has been shown by Gosset, Marie and Meige [4] that the fibers in the median nerve in the arm are divided into four distinct groups. Those for the thenar muscles are on the posterior surface and in contact with the brachial artery. It is probable that selective involvement of these fibers may occur in this area. With Wartenberg, we believe that the paresthesias may be an expression of chronic sensory polyneuritis due to undetermined toxic processes.

SUMMARY AND CONCLUSIONS

Three cases of unilateral partial thenar atrophy are described. They differ from those recently reported in the presence of objective sensory disturbances in all and in the demonstration of sweating disturbances in 2. The atrophy in the first case is possibly the result of brachial neuritis. That in the second case is explicable by direct trauma to the nerve. Although there is no history of infection, intoxication, trauma or pressure in the third case, it is assumed that the atrophy observed in this case, as well as in the others, is due to involvement of selective fibers of the median nerve. Partial thenar atrophy is a benign, nonprogressive condition. It is not related to progressive muscular atrophy, amyotrophic lateral sclerosis, syringomyelia or tumor of the cord.

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2. Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries, New York, Paul B. Hoeber, Inc., 1933.

3. Buzzard, E. F.: Uniradicular Palsies of the Brachial Plexus, Brain **25**:299, 1902

4. Gosset; Marie and Meige, in Tinel, J.: Nerve Wounds, translated by F. Rathwell, New York, William Wood & Company, 1918.

ALCOHOLIC CEREBELLAR DEGENERATION

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AND
H. HOUSTON MERRITT, M.D.
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Considerable confusion exists in the classification of diseases of the cerebellum. There are, however, certain syndromes with clearcut clinical and pathologic characteristics. Among these are the heredodegenerative diseases of Friedreich and Marie, the progressive familial type of cerebellar degeneration of Holmes, the Dejerine-Thomas olivopontocerebellar atrophy and the intracerebellar atrophies.

The intracerebellar atrophies were described by Rossi [1] in 1907 and by Marie, Foix and Alajouanine [2] in 1922. The literature on the subject up to 1933 was collected by Parker and Kernohan.[3] They were able to find 14 cases in the literature, in 11 of which necropsy studies had been made, and reported 1 case of their own. Additional cases have been reported by Brouwer,[4] Maas and Scherer,[5] Hanon,[6] Kennard [7] and de Haene.[8] The clinical symptoms and pathologic picture in all of the reported cases were strikingly constant. The disease was

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Read by title at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 5-7, 1940.

From the Neurological Unit, Boston City Hospital; the Medical Clinic, Peter Bent Brigham Hospital, and the Departments of Neurology and Medicine of the Harvard Medical School.

1. Rossi, I.: Atrophie primitive parenchymateuse du cervelet à localisation corticale, Nouv. iconog. de la Salpêtrière **20**:66-83, 1907.

2. Marie, P.; Foix, C., and Alajouanine, T.: De l'atrophie cérébelleuse tardive à prédominance corticale, Rev. neurol. **38**:849-885 and 1082-1111, 1922.

3. Parker, H. L., and Kernohan, J. W.: Parenchymatous Cortical Cerebellar Atrophy, Brain **56**:191-212, 1933.

4. Brouwer, B.: Beitrag zur Kenntnis der chronischen diffusen Kleinhirnerkrankungen, Neurol. Centralbl. **38**:674-682, 1919.

5. Maas, O., and Scherer, H. J.: Zur Klinik und Anatomie einiger selteren Kleinhirnerkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:420-444, 1933.

6. Hanon, J. L.: La esclerosis del cerebelo en los adultos, Rev. oto-neuro-oftal. **1**:257-283, 1927.

7. Kennard, M. A., cited by Brouwer and Biemond.[9]

8. de Haene, A.: Contribution à l'étude clinique et anatomique de "l'atrophie cerebelleuse tardive à prédominance corticale," J. belge de neurol. et de psychiat. **37**:427-454, 1937.

characterized by a slowly progressive cerebellar syndrome, beginning after middle age in persons with no history of a similar disturbance in other members of the family. The chief difficulty complained of by the patients was in walking, and on examination the signs of cerebellar deficit were symmetric and were most obvious in the lower extremities. Nystagmus was usually absent. Dysarthric speech and a moderate or severe degree of incoordination of the upper extremities were noted in about one-half the cases. The gait was usually described as wide based, and there were marked dysmetria and asynergia in the lower extremities. A slight degree of spasticity of the legs was observed in several of the cases, but usually the reflexes were recorded as normal. The pathologic picture in these cases was characterized by gross atrophy of the cerebellum, particularly in the superior portion of the vermis and the quadrilateral lobule. The posterior and inferior portions of the vermis and the more lateral portion of the lateral lobes were usually less affected. Microscopically, the essential feature was relative or absolute disappearance of the Purkinje cells, with preservation of the basket structures around them. The distribution of the Purkinje cell loss corresponded to the macroscopic atrophy.

Five patients with a clinical picture similar to that described for the intracerebellar cortical atrophy have been studied by us at the Boston City Hospital in recent years. All of the patients were addicted to the prolonged and excessive use of alcoholic beverages. Although we have no autopsy material on these patients, as none have died, it was thought desirable to report the clinical symptoms and to call attention to the role of alcoholism in the production of this syndrome.

REPORT OF CASES

CASE 1.—P. S., a single, unemployed white porter aged 55, was admitted to the Boston City Hospital in May 1935 complaining of unsteadiness of gait for eight years. His past history was not important except for the fact that for many years he had consumed large amounts of beer, whisky, gin and rum, and that his dietary intake had been inadequate. The family history was entirely without significance.

Examination.—General physical examination did not reveal any significant abnormalities. On neurologic examination, there was ataxia in the finger to nose, heel to shin and toe to object tests. The ataxia was most marked in the lower extremities. The gait was staggering, with a broad base. The Romberg sign was positive with the eyes open or closed. The cranial nerves were entirely normal. There was no nystagmus. The reflexes in the arms and legs were normally active; plantar responses were normal, and the abdominal reflexes were present. There was no impairment of cutaneous or deep sensation. The patient was perfectly oriented as to time, place and person. His memory for recent and remote events were good; his mood was even, and there were no evidences of delusions or hallucinations.

The Hinton reaction of the blood was negative; the cerebrospinal fluid was under a pressure of 160 mm. of water; the fluid was clear and colorless and

contained no cells; the protein content was 20 mg. per hundred cubic centimeters, and the colloidal gold and Wassermann reactions were negative.

Course.—The patient has been seen at intervals since 1935 and was last examined on April 1, 1940. During the last five years there has been a slow progression of symptoms, so that now the patient is totally incapacitated for any productive work. He is able to get around the house and take short walks with the aid of a cane. He claims that he drinks very little alcohol at present and notices that the ingestion of even a small amount increases his disability. There has been no essential change in the results of neurologic examination, except that the signs of cerebellar deficit in the lower extremities are more marked. There is marked asynergia in the heel to shin and toe to object tests. The gait shows a very broad base and is ataxic.

Case 2.—T. B., a white, married, unemployed chauffeur aged 36, was admitted to the Boston City Hospital in January 1937 complaining of progressive unsteadiness of the legs for two and one-half years, which had been severe enough to force him to stop working. There had been a slight change in the patient's speech in the last few months. The family history was entirely without significance. The past history was not important except for the fact that he had been addicted to the use of alcoholic beverages in excessive quantities for many years and that his diet had been inadequate.

Examination.—General physical examination gave entirely normal results. The patient was well oriented; his memory was intact; his mood was even, and there were no delusional trends or sense deceptions. Neurologic examination revealed slight inequality of the pupils; both were slightly irregular, but reacted promptly to light and in accommodation. There was nystagmus on lateral gaze to the left. Speech was slightly dysarthric. The gait was wide based and ataxic, and the Romberg test was positive with the eyes open or closed. The finger to nose test showed a slight degree of ataxia, and the heel to shin and toe to object tests revealed marked asynergia and dysmetria. The deep reflexes of the arms and legs were active; the plantar responses were of flexor type, and the abdominal reflexes were present. Muscle tone was slightly increased in the extremities. Cutaneous and deep sensation were normal throughout. The Hinton reaction of the blood was negative; the cerebrospinal fluid was under a pressure of 80 mm. of water; the fluid was clear and colorless and contained no cells; the protein content was 20 mg. per hundred cubic centimeters, and the colloidal gold and Wassermann reactions were negative.

Course.—The patient has been seen at intervals since 1937 and was last examined in April 1940, at which time he was totally incapacitated for any productive work. He is confined to his home and moves about by holding on to the furniture and by using a cane. The physical and neurologic findings at the last examination were the same as on previous occasions.

Case 3.—J. H., a white, single, unemployed laborer aged 41, was referred to the neurosyphilis clinic of the Boston City Hospital in August 1939 because of a positive Hinton reaction of the blood. He had a penile chancre at the age of 17 and had received four injections of arsphenamine. Serologic reactions of the blood were reported as negative at the age of 18. For the past twenty years he had drunk large amounts of alcoholic liquors, averaging more than 1 quart (950 cc.) of hard spirits daily. The diet was usually inadequate. For the past year he had complained of staggering gait and shaking of the hands. The family history was entirely without significance.

Examination.—General physical examination revealed no significant abnormalities; the patient was well oriented, his memory for recent and remote events was good, his mood was even and there were no delusions or sense deceptions. Neurologic examination showed that the left pupil was larger than the right; both were irregular and did not respond to light but reacted actively in accommodation. There were a few unsustained nystagmoid jerks on lateral gaze. There were tremor of the arms in the finger to nose test and some difficulty in performing rapidly alternating movements of the arms. The gait was broad based and ataxic. The heel to shin and toe to object tests showed a marked degree of dysmetria and ataxia. The Romberg test was positive with the eyes open or closed. The deep reflexes of the arms and legs were normally active; the plantar responses were of flexor type, and the abdominal reflexes were present. Cutaneous and deep sensibility were well preserved.

A Hinton reaction of the blood was positive; the cerebrospinal fluid was under a pressure of 130 mm. of water; the fluid was clear and colorless and contained no cells; the protein content was 47 mg. per hundred cubic centimeters; the colloidal gold curve was normal, but the Wassermann reaction was positive. The condition was diagnosed as asymptomatic neurosyphilis and cerebellar degeneration, probably due to alcohol.

Course.—The patient has been receiving weekly treatments for syphilis in the outpatient department but there has been no change in his condition.

CASE 4.—J. B., a white, married, unemployed floorwalker aged 58, was admitted to the Boston City Hospital in April 1935 complaining of gradually increasing unsteadiness of gait for two years. It had progressed to the degree that it was almost impossible for him to walk. The family history was entirely without significance. The past history was not significant except that the patient had drunk more than 1 quart of gin daily for the past twenty years and had apparently had an inadequate diet. He had been admitted to the hospital on three previous occasions for delirium tremens.

Examination.—Physical examination gave normal results except that the blood pressure was 170 systolic and 100 diastolic. The patient was mentally alert and well oriented; there was no gross impairment of memory; the mood was even, and there were no delusions or sense deceptions. On neurologic examination the cranial nerves were normal; there was no nystagmus. There was some clumsiness in performing rapidly alternating movements of the upper extremity, but the finger to nose and finger to finger tests were well performed. The gait was broad based and very unsteady. The Romberg sign was positive with the eyes open or closed, and the heel to shin and toe to object tests showed a marked degree of ataxia. The deep reflexes in the arms and legs were normally active; the plantar responses were of flexor type and the abdominal reflexes were present. Sensory examination, including that of vibratory and position sense, gave normal results. The Hinton reaction of the blood was negative; the cerebrospinal fluid was under a pressure of 120 mm. of water; the fluid was clear and colorless and contained no cells; the protein content was 44 mg. per hundred cubic centimeters, and the colloidal gold and Wassermann reactions were negative.

Course.—The patient has been confined in a hospital for chronic diseases for the past five years; when examined in April 1940 there was no change in his condition except that the difficulty in walking had increased. He is able to get around the ward of the hospital with the aid of a cane.

CASE 5.—F. D., a single, white, unemployed laborer aged 53, was admitted to the Boston City Hospital in February 1936 complaining of unsteadiness of gait for

four years. The disability had progressed in a gradual but unremitting manner. His arms had been affected to a slight degree for the past several years. One and one-half years before admission he noted that his speech was becoming slightly thick. For two months he had been completely unable to walk without support. The family history was entirely without significance. The past history revealed that he had had gonorrheal urethritis twenty years previously, and that he had been addicted to the use of beer and strong alcoholic beverages for many years. He had consumed ½ pint (240 cc.) or more of whisky and from four to six bottles of beer daily. The adequacy of his diet could not be determined.

Examination.—General physical examination gave normal results, except that the blood pressure was 168 systolic and 98 diastolic. The patient was mentally alert and well oriented; his memory for recent and remote events was well preserved; his mood was even, and there were no delusional trends or sense deceptions. Neurologic examination revealed that the cranial nerves were all normal. There was no nystagmus. In the finger to nose test there was a coarse tremor when the nose was approached. Speech was thick and slurred; the gait was broad based, and the patient was able to walk only a few steps before losing his balance. There was marked ataxia in the heel to shin and toe to object tests. Cutaneous and deep sensation were normal. The deep reflexes in the arms and legs were normally active; the plantar responses were of flexor type, and the abdominal reflexes were active. The Hinton reaction of the blood was negative; the cerebrospinal fluid was under a pressure of 100 mm. of water; the fluid was clear and colorless and contained no cells; the protein content was 51 mg. per hundred cubic centimeters, and the colloidal gold and Wassermann reactions were negative.

Course.—The patient was transferred to a hospital for chronic diseases in July 1939 and was last examined in April 1940. He has shown certain defects in memory, which are commensurate with a mild degree of cerebral arteriosclerosis. There has been no change in his physical condition except for the presence of unsustained nystagmus on lateral gaze. He is able to walk around the wards and on the grounds of the hospital with the aid of a cane.

COMMENT

The clinical syndrome presented by these patients is uniform. The family histories were insignificant in all cases. The symptoms were characterized by chronic, progressive cerebellar deficit, which was particularly marked in the lower extremities. All 5 patients were men of Irish extraction, who had been addicted to the use of alcoholic beverages in excessive quantities for many years. The onset of symptoms was in the fourth decade in 1 case, in the fifth decade in 3 cases and the sixth decade in 1 case. The striking feature of the clinical symptoms was that, except for the disturbances in the legs and arms, signs of cerebellar dysfunction were of only minor degree or were entirely absent. There were no mental defects, except in the patient with arteriosclerosis, and no changes in the reflexes or disturbances of sensation.

The cerebellar syndrome in these cases corresponds in all details with that in the cases described by Marie, Foix and Alajouanine [2] and in those collected by Parker and Kernohan.[3] The causes of the cerebellar degeneration in the cases reported in the literature were not uni-

form. Several authors emphasized the importance of antecedent illnesses, including cancer and syphilis,[9] and in several instances alcohol was stressed as an etiologic factor, particularly in the case described by Thomas [10] and in that reported by Stender and Lüthy.[11] The patient in the last case had experienced three episodes of delirium tremens and had had typical alcoholic polyneuritis several years before the onset of the cerebellar signs. In the cases reported by Lhermitte [12] and de Haene [8] the patients also had chronic alcoholism.

It is interesting to note that destruction of Purkinje cells by alcoholic intoxication in animals has been produced by Lhermitte,[12] in collaboration with Kulikowsky, and by Lhermitte and others.[13] This destruction of Purkinje cells is probably the same as that observed in patients with intracerebellar atrophy.

The patient reported on by Thomas [10] had had syphilis prior to the onset of the cerebellar signs. One of our patients (case 3) had pupillary abnormalities indicative of syphilis of the central nervous system, and there was a positive Wassermann reaction of the cerebrospinal fluid. We are of the opinion that the degeneration of the cerebellum in this patient is more closely related to his chronic alcoholism than to his syphilitic infection.

The importance of the diet in cases of chronic alcoholism is well known. It is difficult to obtain an adequate history of the diet from such patients, but 4 of our patients had a definite history of an inadequate dietary intake over a prolonged period, and in only 1 patient did this factor seem not to be significant. In none of the patients were there signs of edema, pellagra or peripheral neuritis. In the absence of autopsy material, we can only postulate that the pathologic picture in our cases is similar to that previously described, that is, atrophy of the Purkinje cells in the cerebellum. If chronic alcoholism is the cause of atrophy in these cases, the mechanism of the production of the lesion can only be conjectured. Whether it is a direct effect of the alcohol on these cells or whether a concomitant nutritional deficiency is the main factor is not known.

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9. Brouwer, B., and Biemond, A.: Les affections parenchymateuses du cervelet et leur signification du point de vue de l'anatomie et de la physiologie de cet organe, J. belge de neurol. et de psychiat. **38**:691-757, 1938.

10. Thomas, A.: Atrophie lamellaire des cellules de Purkinje, Rev. neurol. **13**:917-924, 1905.

11. Stender, A., and Lüthy, F.: Ueber Spätatrophie der Kleinhirnrinde bei chronischen Alkoholismus, Deutsche Ztschr. f. Nervenh. **119**:604-622, 1931.

12. Lhermitte, J.: Cortical Cerebellar Degeneration, Proc. Roy. Soc. Med. **28**:379-390, 1935.

13. Lhermitte, J.; de Ajuriaguerra, J., and Garnier: Les lésions du système nerveux dans l'intoxication alcoolique expérimentale, Compt. rend. Soc. de biol. **128**:386-388, 1938.

SUMMARY

The clinical description of 5 male patients with gradually progressive cerebellar ataxia involving principally the lower extremities is presented. The onset occurred in middle life, after many years of excessive alcoholic intake. The family histories were without significance. The symptoms were uniform. In addition to the cerebellar ataxia in the lower extremities, nystagmus was present in 2 patients, speech disturbance in 2 and a slight or moderate degree of cerebellar ataxia in the upper extremities in 4. There were no evidences of lesions of the pyramidal tract, posterior column or peripheral nerve in any of the patients. One patient had neurosyphilis, as evidenced by abnormal pupils and a positive Wassermann reaction of the cerebrospinal fluid.

We believe that the condition of these patients resembles the cerebellar syndrome described as cortical or intracerebellar atrophy. Moreover, we believe that alcohol or an associated nutritional disturbance is a significant factor in the development of this syndrome.

VASCULAR CHANGES IN THE THALAMIC NUCLEI UNDERGOING RETROGRADE DEGENERATION

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The different parts of the neocortex receive fibers from definite cell masses in the dorsal thalamus. Injury to a cortical area results in retrograde degeneration of the thalamic center the fibers of which end in the area destroyed. Associated with the degeneration of the nerve elements there occur profound vascular changes. This was first noticed in the dorsal nucleus of the lateral geniculate body after extirpation of the visual cortex.[1] The vascular changes consisted of enlargement of the afferent vessels, apparent increase in their number, thickening of the capillary network and heightened permeability of the vascular walls.

The present study is an attempt to find whether there are such vascular changes in other thalamic nuclei after destruction of their respective cortical fields. I used albino rats as subjects. The projection of the thalamic centers on the cortex in this animal has been worked out by Lashley,[2] Clark,[3] Clark and Boggon[4] and Waller.[5] In the light of the cortical areas as mapped by these authors, particularly the last mentioned, I removed the projection fields for the medial geniculate body, the centrum medianum and the ventral and lateral nuclei. The lateral geniculate body has been separately studied and reported on. The anterior group of thalamic nuclei, the axons of which project too diffusely to the cingular area on the medial surface of the hemisphere, was not considered. After varying periods of degeneration the blood vessels of the experimental brains were injected with a colored medium for microscopic study.

From the Department of Anatomy of the Peiping Union Medical College.

1. Tsang, Y. C.: Vascular Changes in the Lateral Geniculate Body Following Extirpation of the Visual Cortex, Arch. Neurol. & Psychiat. **36**:569 (Sept.) 1936.

2. Lashley, K. S.: (*a*) The Mechanism of Vision: IV. The Cerebral Areas Necessary for Pattern-Vision in the Rat, J. Comp. Neurol. **53**:419 (Dec.) 1931; (*b*) The Mechanism of Vision: VIII. The Projection of the Retina upon the Cerebral Cortex of the Rat, ibid. **60**:57 (Aug.) 1934.

3. Clark, W. E. L.: An Experimental Study of Thalamic Connections in the Rat, Phil. Tr. Roy. Soc., London, s.B **222**:1, 1932.

4. Clark, W. E. L., and Boggon, R. H.: On the Connections of the Anterior Nucleus of the Thalamus, J. Anat. **67**:215 (Jan.) 1933.

5. Waller, W. H.: Topographical Relations of Cortical Lesions to Thalamic Nuclei in the Albino Rat, J. Comp. Neurol. **60**:237 (Oct.) 1934.

Waller's terminology was followed throughout to facilitate comparison with his cellular study of the thalamic centers undergoing retrograde degeneration.

METHOD

Eight adult albino rats were used. With the animal under ether anesthesia and with aseptic precautions, a hole was made in the skull by means of an electric trephine, 2 mm. in diameter. Through the hole a part of the cortex was

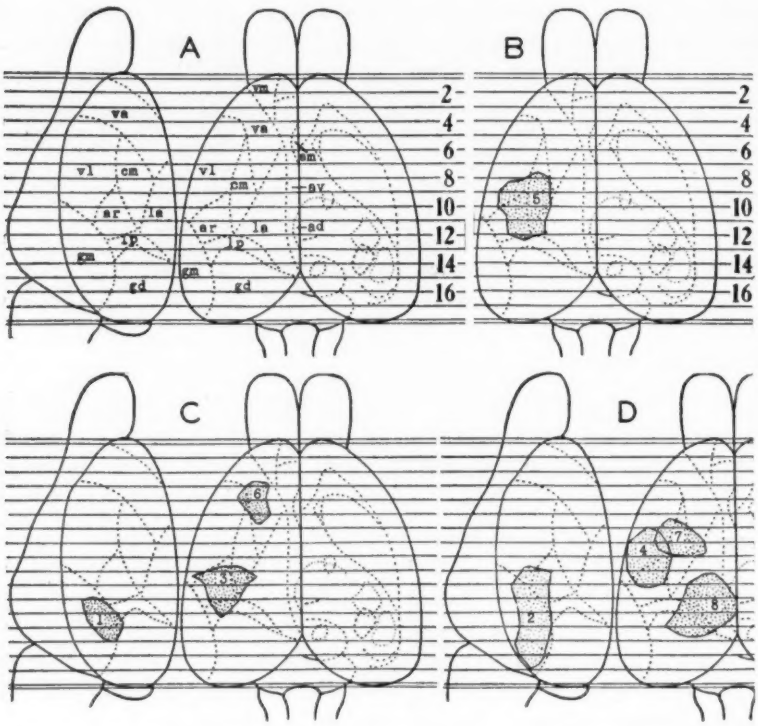

Fig. 1.—Reconstructions of the cerebral lesions in the experimental animals. *A* is Lashley's modification of Waller's map of the thalamocortical projection areas in the rat, with reference to which the lesions were inflicted. The shaded parts in *B*, *C* and *D* represent the reconstructed lesions in the individual rats, denoted by the enclosed numerals.

In this figure and in the accompanying figures, the following abbreviations appear: *ad*, anterodorsal nucleus; *am*, anteromedial nucleus; *ar*, arcuate nucleus; *av*, anteroventral nucleus; *cc*, corpus callosum; *ce*, central nucleus; *cf*, column of the fornix; *ch*, optic chiasm; *cm*, centrum medianum; *cs*, corpus striatum; *gd*, dorsal nucleus of the lateral geniculate body; *gm*, medial geniculate body; *h*, hippocampus; *ha*, habenular nuclei; *hy*, hypothalamus; *la*, lateral anterior nucleus; *lp*, lateral posterior nucleus; *m*, medial nucleus; *mt*, mamillothalamic tract; *nc*, neocortex; *p*, cerebral peduncle; *pc*, paracentral nucleus; *pt*, paratenial nucleus; *pv*, paraventricular nucleus; *re*, reuniens nucleus; *rt*, reticular nucleus; *st*, stria terminalis; *to*, optic tract; *v*, lateral ventricle; *va*, ventroanterior nucleus; *vl*, ventrolateral nucleus, and *vm*, ventromedial nucleus.

destroyed by extirpation or by cauterization. The destructions were made with reference to the projection fields for the various thalamic nuclei as mapped by Waller (fig. 1 *A*). A single lesion was inflicted in the left hemisphere in each case. The wound was superficial, subcortical structures being avoided.

The period of degeneration varied from seventeen to twenty-two days. The vascular system of the brain was injected with a mixture of carmine and gelatin through the ascending portion of the aorta by means of a pressure bottle. The heated mixture was preceded by physiologic solution of sodium chloride with the addition of a little sodium nitrite to wash and dilate the blood vessels. The injected brain was fixed in situ in a dilute solution of formaldehyde U. S. P. (1 : 10).

Pyroxylin sections of 150 and 30 microns were cut alternately and mounted in series on separate slides. The thin sections were stained for cells with cresyl violet, while the thick ones were not stained at all. These parallel series of sections showed the cellular and the vascular conditions in the degenerated thalamic centers.

On the basis of the stained sections selected at fixed intervals, the lesions in the cortical fields were reconstructed on Lashley's modification of Waller's chart of the cortical areas for the rat (fig. 1 *B, C* and *D*).

RESULTS

Destruction of the cortical areas in the experimental animals invariably induced vascular disturbances in their corresponding thalamic nuclei. The nature and extent of these changes varied with the thalamocortical systems concerned. I shall, therefore, treat the thalamic nuclei separately.

The Medial Geniculate Body.—Rats 1 and 2 were deprived of the auditory areas of the left hemisphere (fig. 1 *C* and *D*). There resulted profound vascular changes in the medial geniculate body on the same side, together with cellular degeneration. The condition in rat 1 was especially striking (fig. 2 upper part). The vessels supplying this area were enormously enlarged; the extraordinary caliber of some of them has never been met in a normal structure. The walls of the vessels became highly permeable to carmine, so that a large amount of the dye was diffused through the nucleus. The capillary network was enriched. This was the consequence of one or both of two factors. In normal nerve tissue a number of the capillaries are in a collapsed condition and are not readily distended by the contrast medium. Pathologic reactions make them more susceptible to injection. The formation of new capillaries from the old ones is apparently possible even in the central nervous system under pathologic influences, just as in other body tissues.

The medial geniculate body on the left, and affected, side in rat 2 showed similar changes in its vascular system, but to a lesser degree.

The vascular changes in the medial geniculate body undergoing retrograde degeneration were comparable in every respect with those in the lateral geniculate body following extirpation of the visual cortex. An explanation of this similarity will be given later.

The Ventral Thalamic Nuclei.—Included in this group are the arcuate, the ventrolateral, the ventroanterior and the ventromedial nucleus of the thalamus.

(*a*) The Arcuate Nucleus (*ar*): This is a broad band of fairly large and closely packed cells. It is situated ventromedial to the lateral geniculate body. The lesion in rat 3 involved its projection area as determined by Waller (fig. 1 *C*).

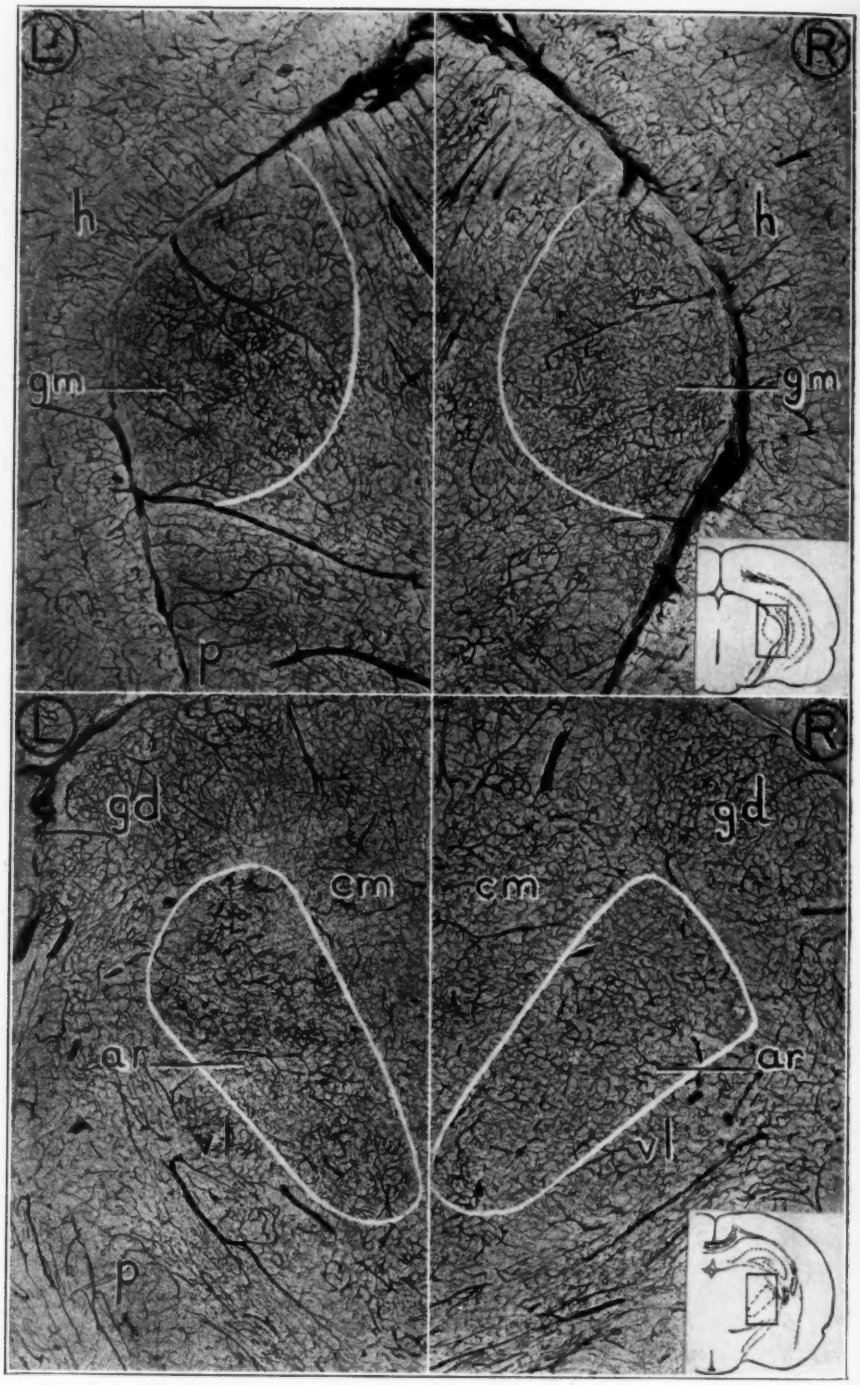

Figure 2

(See legend on opposite page)

The degeneration of this nucleus was complete, the outlines of the ganglion cells being hardly perceptible. The vascularity of the affected nucleus was obviously increased. The blood vessels were enlarged; the capillary network was thickened, and the perivascular diffusion of carmine was pronounced. Figure 2 (lower parts) shows the vascular condition of the degenerated left nucleus, in contrast to that of the normal structure on the right side.

The lesions in rats 4 and 5 partly invaded the projection area of the arcuate nucleus (fig. 1 *B* and *D*). The vascular system of this nucleus in rat 4 showed marked changes similar to those in rat 3, as reproduced in the photomicrograph. The extent of these disturbances is indicated in figure 3. The vascular disturbances in the arcuate nucleus in rat 5 were focused in its lateral region (fig. 3). The dilatation of the vessels and the diffusion of carmine were especially noticeable.

(*b*) The Ventrolateral Nucleus (*vl*): This nucleus is a flat mass of scattered large cells between the arcuate and the reticular (*rt*) nucleus, being intimately associated with the former. The lesion in rat 4 (fig. 1 *D*) brought about the complete degeneration of this nucleus, while that in rat 5 (fig. 1 *B*) affected only its lateral edge. The vascular disturbances were coextensive with the cellular degeneration (fig. 3). The enlargement of the vascular caliber and the infiltration of carmine were the conspicuous features. The number of capillaries was apparently not increased.

(*c*) The Ventroanterior Nucleus (*va*): This nucleus is a mass of large cells in front of the arcuate and medial to the reticular nucleus. The removal of the middle part of Waller's area *va* in rat 6 (fig. 1 *C*) resulted in cellular degeneration and vascular disturbances in the medial part of this nucleus (fig. 3). After extirpation of the caudal region of area *va* in rat 7 (fig. 1 *D*), the lateral part of the anterior half of this nucleus was the focal point of the vascular changes (fig. 3). Dilatation of the blood vessels and infiltration of carmine were recognizable in both cases.

(*d*) The Ventromedial Nucleus (*vm*): Although the lesion in rat 6 was largely confined to Waller's area for the ventroanterior nucleus (fig. 1 *C*), cellular degeneration and vascular changes similar to those in the preceding cases occurred in the ventromedial nucleus (fig. 3). This is explicable by the anatomic intimacy that exists between the two nuclei.

The Centrum Medianum.—This is an ill defined cell group dorsomedial to the arcuate nucleus. Its cells are small and dispersed. Its cortical area (*cm*) was

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EXPLANATION OF FIGURE 2

Fig. 2.—Photomicrographs (upper) of the medial geniculate bodies in one and the same section taken from rat 1. The heavy white line marks the medial boundary of this structure. The insert indicates the region reproduced. The left (*L*) nucleus underwent retrograde degeneration; the right (*R*) was normal. The vascularity of the former is evidently increased. The dark background is due to the diffusion of carmine through the vascular walls as well as to the thickening of the capillary network. Carmine-gelatin injection. × 35.

Photomicrographs (lower) of the arcuate nuclei in one and the same section taken from rat 3. The heavy white line marks the boundary of this structure. The insert indicates the region reproduced. The left (*L*) nucleus underwent retrograde degeneration; the right (*R*) was normal. The former shows increased vascularization with perivascular infiltration of carmine. Carmine-gelatin injection. × 35.

damaged in rats 3, 5 and 7 (fig. 1 *B, C* and *D*), but only in rat 5 did vascular disturbances appear in the anterior part of the nucleus, evidenced chiefly by increase in vascular caliber and diffusion of carmine (fig. 3). The inconsistency of the vascular changes in this nucleus will be discussed later.

The Lateral Nuclei.—This group consists of an anterior (*la*) and a posterior (*lp*) nucleus, with no definite boundary between them. They are dorsomedial to the dorsal nucleus of the lateral geniculate body throughout. The lesion in rat 8

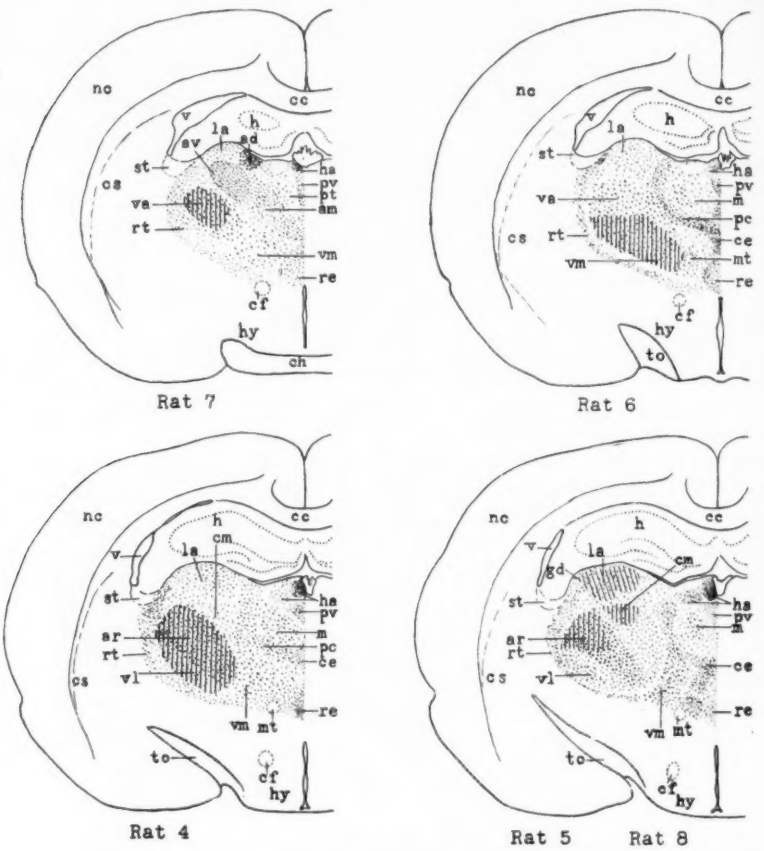

Fig. 3.—Representative cross sections of the brains of the rats, with the most extensive vascular changes in the degenerated thalamic nuclei. The affected regions are shaded with parallel lines. In rat 4 the arcuate (*ar*) and the ventrolateral (*vl*) nuclei are involved; in rat 5, the centrum medianum (*cm*), in addition to the two nuclei just mentioned; in rat 6, the ventroanterior (*va*) and ventromedial (*vm*) nuclei; in rat 7, the ventroanterior nucleus (*va*), and, finally, in rat 8, the lateral anterior nucleus (*la*).

fell largely within areas *la* and *lp*, besides involving partly the neighboring fields (fig. 1 *D*). The lateral anterior nucleus, the rostral half of the lateral posterior nucleus and the medial part of the dorsal nucleus of the lateral geniculate body were degenerated. The vascular changes were more pronounced in the lateral

anterior nucleus, and manifested themselves in dilatation of the blood vessels, perivascular diffusion of carmine and increase in number of the capillaries. The extent of the vascular disturbances in this and in the adjacent nuclei is indicated by the parallel oblique lines in figure 3.

COMMENT

Destruction of parts of the neocortex induces degenerative reactions in the thalamic nuclei, axons of which project to the cortical parts removed. The reactions start with axonal chromatolysis and culminate in disappearance of the cells. The products of nerve decomposition are noxious and demand prompt removal. The blood vessels, together with their contents, play a prominent role in clearing up the site of degeneration. The vessels are enlarged to allow an increased flow of blood and efficient drainage of the products of disintegration. The vascular wall becomes unusually permeable, so that the liquids from the blood stream readily penetrate the surrounding tissue and leukocytes and other wandering cells migrate freely through the endothelial wall to reach the affected region. It seems established that in nerve tissue suffering from injuries or undergoing degeneration the capillaries multiply rapidly.[6] This means an increase in blood supply per unit volume of tissue. All these circulatory changes contribute to augment the blood flow and to remove and detoxicate the injurious debris.

The relative severity of the vascular disturbances in the different thalamic nuclei needs comment. The disturbances were greatest in the medial geniculate body and slight in the centrum medianum, the ventral and lateral nuclei being intermediate in this respect. The explanation of this difference lies in the distribution of the thalamic projection fibers in the cortex. The ascending fibers from the lateral and the medial geniculate body focalize, respectively, in the visual and the auditory areas,[7] destruction of which results in concentrated cellular and vascular changes in the geniculate bodies. The case of other nuclei is different. The axons of the ventral and lateral nuclei and of the centrum medianum are distributed diffusely to the somesthetic cortex. No definite boundaries exist between their respective projection areas. The somesthetic cortex constitutes about two thirds of the total surface of the hemisphere (Waller's areas *ar, vl, va, vm, cm, la* and *lp,* fig. 1 A). This vast field, except areas *vl, ar* and *lp,* is electrically stimulable.[8]

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6. Tsang, Y. C.: Vascular Changes Following Experimental Lesions in the Cerebral Cortex, Arch. Neurol. & Psychiat. **35**:1280 (June) 1936; footnote 1.

7. Pennington, L. A.: The Function of the Brain in Auditory Localization: II. The Effect of Cortical Operation upon Original Learning, J. Comp. Neurol. **66**:415 (April) 1937. Lashley.[2b]

8. Lashley, K. S.: Studies of Cerebral Function in Learning: III. The Motor Areas, Brain **44**:255 (Nov.) 1921.

Droogleever Fortuyn,[9] Herrick [10] and Lashley [11] long ago pointed out that the somesthetic and motor areas of the rat overlap extensively, and that these cortical types have attained only incipient differentiation. Consequently, the extirpation of a limited cortical field usually brings about partial degeneration and moderate vascular changes in the corresponding somesthetic nuclei. The cortical connections of the centrum medianum are perhaps the most diffuse of all; the vascular changes accompanying its cellular degeneration can only occasionally be revealed.

The visual and auditory areas are the ones most exactly localized in the rat. The concentrated vascular disturbances in the geniculate bodies after removal of these areas reflect the exactness of their localization. Vascular changes paralleling cellular degeneration in the somesthetic nuclei following destruction of their cortical fields as determined by Waller also indicate the general accuracy of his mapping. Thus, the positive vascular disturbances in the thalamic nuclei, as revealed by the injection technic, serve to corroborate the localization of their cortical areas by means of degeneration methods.

SUMMARY

The projection areas on the left hemisphere for the medial geniculate body, the ventral and lateral thalamic nuclei and the centrum medianum were destroyed in 8 adult albino rats. Seventeen to twenty-two days after the operation, the blood vessels of the experimental brains were injected with a carmine-gelatin mixture. The thalamic nuclei were studied microscopically, with the following results.

The thalamic nuclei undergoing retrograde degeneration showed generally an increase in vascularization. This manifested itself in enlargement of the blood vessels and multiplication of the capillaries. The vascular wall became highly permeable to carmine, so that heavy perivascular infiltrations were invariably present. The relative prominence of these changes varied with the different animals.

In the thalamic nuclei the ascending fibers from which focalize in a small cortical area greater vascular changes developed than in those the axons of which project diffusely to wide cortical fields. The medial geniculate body showed the severest vascular disturbances; the ventral and lateral thalamic nuclei came next; the centrum medianum was the least affected.

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9. Droogleever Fortuyn, A. B.: Cortical Cell-Lamination of the Hemisphere of Some Rodents, Arch. Neurol. & Psychiat., London **6**:221, 1914.

10. Herrick, C. J.: Brains of Rats and Men, Chicago, University of Chicago Press, 1926.

11. Lashley, K. S.: Brain Mechanism and Intelligence, Chicago, University of Chicago Press, 1929.

The vascular changes are interpreted as measures for increasing the blood flow and for removing and detoxicating the products of nerve disintegration.

In the light of the vascular changes induced in the thalamic nuclei by destruction of their cortical fields, Waller's localization of the cortical areas for the few thalamic nuclei in question is correct in a general way.

The present study was carried out under a research fellowship in the department of anatomy (Prof. A. B. Droogleever Fortuyn, head) of the Peiping Union Medical College.

A THIRTEEN YEAR FOLLOW-UP STUDY OF A SERIES OF CASES OF VERIFIED TUMORS OF THE BRAIN

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In the past few years an opportunity arose to gather carefully compiled data on the results of operations on the brain performed by Dr. Harvey Cushing in the year Oct. 1, 1925 to Oct. 1, 1926, during my term as resident in neurosurgery at the Peter Bent Brigham Hospital. The painstaking follow-up system which Dr. Cushing maintained, with the assistance of Dr. Louise Eisenhardt, over many years has made this task relatively simple. Similar investigations have already been made by my predecessor, Dr. Van Wagenen,[1] who was resident during 1924-1925, and by my successor, Dr. Cairns,[2] who filled this position in 1926-1927. My report, therefore, will complete the investigation of the late results (after from seven to fourteen years) in a series of cases in which operations were performed during a period of three consecutive years, from Oct. 1, 1924 to Oct. 1, 1927. Since the data based on the work of a single year may be inadequate to give a true picture of the object in view. free use will be made of the facts included in the papers of Van Wagenen and Cairns.

The three years represented an unusual period of transition in neurosurgery, since they include the time just before, during and just after the introduction of electrosurgery into this field. The late results for this period may, therefore, be looked on as a fair sample of the eventual outcome of neurosurgical therapy as applied to cerebral tumors by Dr. Cushing.

As already stated in the previous papers, the object of this investigation is not only to determine the mortality rate and the period of survival, but also to gain some information concerning the degree of usefulness, both social and economic, of the patients who survived. Dr. Cushing[3] published a monograph covering the case and operative mortalities in

1. Van Wagenen, W. P.: Verified Brain Tumors: End Results of One Hundred and Forty-Nine Cases Eight Years After Operation, J. A. M. A. **102**:1454-1458 (May 5) 1934.

2. Cairns, H.: The Ultimate Results of Operations for Intracranial Tumors, Yale J. Biol. & Med. **8**:421-491, 1936.

3. Cushing, H.: Intracranial Tumours, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

over 2,000 cases in which he performed operation from 1901 to 1931. This, of course, includes the material in this report and those of Van Wagenen and Cairns. Dr. Eisenhardt [4] also presented a review of the same material from the angle of the patients who survived for five years or more after operation, up to 1935.

By combining data from these two studies, it will be possible to gain some idea of the number of patients who survived for five years or more in each tumor group of the whole Cushing series. This will be done for each type of tumor for purposes of comparison with the segment of the series under discussion here.

During the year Oct. 1, 1925 to Oct. 1, 1926, 152 patients were operated on and the tumors verified. Some of the patients had been operated on one or more times before, and some have been operated on one or more times in subsequent years. Up to the time of writing, 211

TABLE 1.—*Ultimate Results in Four Hundred and Fifty-Seven Cases of Intracranial Tumors Operated on During 1924-1925,*[1] *1925-1926 and 1926-1927* [2]

Type of Tumor	Patients Who Died	Patients Living 7-14 Years After Operation	Total No. of Patients
Gliomas	163	36	199
Pituitary adenoma	28	59	87
Meningioma	34	31	65
Neurinoma	16	24	40
Craniopharyngioma	19	4	23
Tumors of blood vessels	4	5	9
Metastatic carcinoma	17	0	17
Miscellaneous	6	11	17
Total	287	170	457

operations had been performed on the 152 patients. Of the total number, 27 patients died before leaving the hospital after the operation. Thus, 125 remain, and the postoperative course of these patients will be studied in this paper. Of these, 78 patients died in from a few months to seventeen years after the first operation, leaving 47 who were still alive from thirteen to more than fourteen years after the operation in 1925-1926. These figures are included in table 1, which summarizes the total results for the years 1924 to 1927; from these data it is evident that somewhat less than a third of the patients operated on still survived at the time these investigations were made. Many of the patients who were dead at the time that these studies were made had nevertheless survived for a number of years after operation; the period of survival, expressed in years, for patients with the different types of tumors during the year 1925-1926 is shown in table 2.

4. Eisenhardt, L.: Long Postoperative Survivals in Cases of Intracranial Tumors, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:390-416, 1937.

GLIOMAS

While the general statement, as demonstrated in tables 1 and 2, is revealing, a truer conception of the results of neurosurgical treatment can be obtained only by a closer examination of cases of the individual types of tumors. The gliomas, for example, include not only the least

TABLE 2.—*Intracranial Tumors Occurring During 1925-1926: Duration of Life, in Years, from Time Tumor Was First Removed*

Type	Total No. of Patients	Period Before Death, Years: Post-operative	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-15	Patients Still Living	Patients Not Reported
Gliomas	62	14	16	5	6	3	3	3	..	..	..	..	..	12	..
Pituitary adenoma	33	3	..	1	2	1	1	3	1	2	1	2	2	14	..
Meningioma	18	2	4	1	..	..	..	..	..	1	1	..	2	7	..
Neurinoma (acoustic)	19	2	..	2	1	2	..	..	..	1	..	..	1	9	1
Craniopharyngioma	12	2	3	1	2	..	..	..	1	..	..	..	..	2	1
Tumors of blood vessels	1	0	..	..	..	..	..	..	..	..	..	..	..	1	..
Metastatic carcinoma	5	4	1	..	..	..	..	..	..	..	..	..	..	..	..
Miscellaneous	2	..	..	..	..	..	..	..	..	..	..	..	..	2	..

TABLE 3.—*Gliomas Occurring During 1925-1926: Duration of Life, in Years, Calculated from Time Tumor Was First Removed*

Type of Tumor	Total No. of Patients	Period Before Death, Years: Post-operative	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10+	Patients Still Living
Glioblastoma multiforme	12	2	6	..	3	1	..	..	..	..	..	..	..	0
Medulloblastoma														
Cerebellar	3	2	1	1	..	..	..	1	..	..	..	..	..	..
Cerebral	2	..	1	..	..	..	1	..	..	..	..	..	..	..
Oligodendroglioma	3	1	..	..	..	..	1	..	..	..	..	..	..	1
Cyst only	5	..	2	..	1	..	1	..	..	..	..	..	..	1
Astroblastoma	6	1	..	..	1	1	..	2	..	..	..	..	..	1
Atypical glioma	3	1	1	1	..	..	..	..	..	..	..	..	..	..
Ependymoma	3	..	..	..	..	..	..	..	..	..	..	..	..	3
Spongioblastoma polare	4	1	1	..	..	..	..	..	..	..	..	..	..	2
Papilloma	2	1	..	..	..	..	..	..	..	..	..	..	..	1
Astrocytoma														
Cerebellar	7	2	..	1	..	..	..	..	..	..	..	..	1	3
Cerebral	12	3	3	1	1	2	..	..	..	..	..	..	..	2

favorable but also the most favorable lesions in the whole series of tumors of the brain. As will be seen from table 3, glioblastoma multiforme is still by far the most malignant and most rapidly fatal primary tumor of the brain. However, not only can the astrocytoma occurring in the cerebellum in children be removed apparently completely but, after its removal, the permanence of the cure and the postoperative duration of life, as first pointed out by Van Wagenen, are definitely better even than in cases of the meningiomas.

GLIOBLASTOMA MULTIFORME

Fifteen patients with glioblastoma multiforme were admitted during the year under investigation. Of these, 3 died before operation could be undertaken and the lesions were verified at necropsy. The 12 patients who were operated on are all long since dead. Two died immediately after operation; 6 died in less than one year; 3 survived between two and three years, and only 1 lived three and one-half years. The data for the preceding and the following year yield similar results. In 1924-1925, there were 21 patients with this tumor, whose average duration of life after operation was twelve months. In 1926-1927 there were 8 patients, of whom 6 died within a year and 2 survived from one to two years. There were 208 cases of glioblastoma multiforme in Dr. Cushing's whole series, and the unfavorable character of this tumor is indicated by the absence of a single case in Eisenhardt's report on patients who survived five years or more after operation.

Throughout the three years, the experience with this type of tumor was constant. The lesion usually occurred in adults, often those past middle age, and more frequently in males. The course was commonly short and fulminating. Whether the lesion was removed only partially or macroscopically in toto, recurrence was rapid, and secondary operation, which was carried out in 6 cases in 1925-1926, did little to extend the life span of the patient, and even less to promote his comfort during the period of survival. With the exception of 1 patient with a useful period of activity as a physician for over three years, the average period of useful, or even comfortable, existence after operation was about half that of survival. The tumors were all rather large, and in 5 of the 12 cases contained large cystic cavities. Histologically, they showed multiple types of cells, large areas of necrosis and usually hyperplasia of the adventitial layer of the blood vessels.

Two cases in the series were sufficiently exceptional to deserve citation. One was that of a typical glioblastoma multiforme, which occurred, however, in a boy aged 7. The other was that of a physician who survived for over three years and continued his practice as a specialist throughout this period. Being himself a radiotherapeutist, he took an unknown, but very large, quantity of roentgen radiation.

Cairns has adequately, if somewhat gloomily, presented the helplessness of the surgeon in dealing with this lesion. However, as he pointed out, one cannot refuse to operate, since the clinical diagnosis cannot as yet be made with certainty and since occasionally when a glioblastoma multiforme is suspected a more benign lesion is found. The experience with the possible effect of roentgen rays in the case in which the survival period was three and one-half years may be significant, and an adequate way of dealing with this tumor may await the day when newer methods of applying roentgen radiation and other physical, and perhaps chemical, agents are developed.

MEDULLOBLASTOMA

There were only 5 cases of medulloblastoma in the 1925-1926 series, in 1 of which the tumor involved the cerebrum of an adult. This patient was subjected to a series of three operations and survived for four years and eleven months after the first operative procedure. Because of convulsive seizures, he was prevented from returning to his former occupation, but was partially restored to activity for three years after the first operation and for six months after the second. In 1924-1925 no cases of this tumor in the cerebrum were encountered, and in 1926-1927, 2 were described. One of the patients survived five months and the other nearly five years after the operation.

Of the characteristic midline cerebellar medulloblastoma occurring in children, there were 4 cases in 1925-1926. One of these was the celebrated case of Jackie Hogan, described by Cushing,[5] who had five operations and lived for five years and three months after the first procedure. For four years after the first operation and a series of roentgen treatments he attended school and was a fairly normal child. The lesion then recurred rapidly, in spite of combined heroic surgical intervention and considerable radiation. The remaining 3 patients survived for an average of nine months. In 1924-1925, 17 persons with this tumor were operated on, with an average survival period of fourteen and five-tenths months, and in 1926-1927 there were 5 patients, with an average survival period of thirteen months. Thus it will be seen that for the three year period there was a total of 26 cases of cerebellar medulloblastoma occurring in children, all of whom had died at the time of these studies. Indeed, only 1 patient had survived for over five years, during which time he was operated on five times. The remaining 25 patients showed an average survival period of only thirteen and five-tenths months.

In spite of the poor prognosis, this is the only tumor in the glioma group in which the evidence of the beneficial effects of roentgen radiation is unequivocal. Elsberg and Gotten[6] have shown that mere suboccipital decompression followed by irradiation is followed by as long a period of survival as in cases in which the roentgen therapy is given after radical surgical excision. Indeed, Cutler, Sosman and Vaughan[7] advocated irradiation without operation in cases of cerebellar medulloblastoma. The one weakness in the attitude of the latter authors is that the diagnosis can never be made with absolute certainty, and a benign lesion may be allowed to produce irremediable effects before the error is corrected. Fundamentally, however, the hopelessness of this disease lies in the fact that radiosensitivity eventually disappears and then nothing can prevent the seeding of the tumor throughout the cerebrospinal fluid spaces and death. In a total of 86 cases in Cushing's series, 6 patients survived five years or more after operation, and of these 3 were adults with the tumor located in the cerebrum.

ASTROBLASTOMA

The astroblastoma is a relatively uncommon tumor and occurred in 6 cases in this series. The patients ranged from 12 to 43 years of age, and, except for the girl aged 12, whose tumor was located in the third ventricle and who is still alive thirteen years after operation, have all long since died. The period of survival for the group averaged four years and ten months. Most of the patients had several operations, and none were restored to complete health, although 1 person who had three operations in as many years carried on as an expert photographer between these procedures in spite of varying degrees of aphasia and right hemiplegia. Another in the series was fairly well for one year after operation, and the girl with the tumor in the third ventricle, although sluggish mentally and suffering from almost weekly seizures, enjoys playing and singing and leads a relatively comfortable existence.

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5. Cushing, H.: Experiences with the Cerebellar Medulloblastomas: A Critical Review, Acta path. et microbiol. Scandinav. **7**:1-86, 1930.

6. Elsberg, C. A., and Gotten, N.: The Results of Conservative Compared with Radical Operations in the Cerebellar Medulloblastomas, Bull. Neurol. Inst. New York **3**:33-52, 1933.

7. Cutler, E. C.; Sosman, M. C., and Vaughan, W. W.: The Place of Radiation in the Treatment of Cerebellar Medulloblastoma, Am. J. Roentgenol. **35**:429-453, 1936.

During Van Wagenen's term, 3 cases of astroblastoma were encountered, with an average period of survival of twenty-four months and an average period of usefulness of twelve months. Cairns reported 4 cases, with survival periods of three months, thirteen months, four and a half years and nine years, respectively. The last patient was still alive at the time of the report, and for all intents and purposes completely cured. Thus, for the three year period between 1924 and 1927, 13 patients with astroblastoma were treated surgically. Two of the patients were still alive at the time of the investigations, nine and eleven years after operation. The one was apparently cured; the other was an invalid but was leading a comfortable existence. The average duration of life for the entire group was three years and nine months, and the average period of usefulness was less than half this length and was generally marred by serious disabilities. Four of Dr. Cushing's 35 patients survived five years or more after operation, and 2 of them were alive at the time of Dr. Eisenhardt's report, ten and twelve years after operation.

ASTROCYTOMA

Cerebral.—According to the precedent set by Van Wagenen and Cairns, the gliomatous tumors, consisting largely of mature astrocytes, may be divided into (1) those occurring in the cerebrum of mature adults, and (2) those occurring in the cerebellum of children or young adults. Of the former, there were 12 cases in the present series, in 3 of which the patient died in the hospital after operation. In the other 9 cases the average period of survival was five years two and one-half months. In 2 of this group the patients were still alive thirteen years and two months, respectively, after the original operation. On 1 of them, however, a boy, aged only 8 at the time of the first operation, secondary operations were performed at another hospital three, six and thirteen years later. At the time of this survey he was 22 years of age and showed no evidence of recurrence of the tumor, although he bore the burden of left homonymous hemianopia and slight hemiparesis and occasionally suffered from tingling sensations in the left hand.

The second surviving patient was a woman aged 22 with a cyst and mural tumor in the left lateral ventricle; these were removed by way of a transcortical incision. In spite of this, she had only transient aphasia and right homonymous hemianopia, which largely disappeared before she left the hospital. She has remained well since, except for one or two momentary "weak" spells. She married six months after operation and is raising a sturdy son.

There were 13 cases of cerebral astrocytoma in the year preceding and 15 in the year following the present study. In the first group no patient was living at the time of the survey, and in the latter 1 survived for nine years, another was still living at the time of the review and a third died about seven years after the operation. Thus, 40 patients with astrocytomatous tumors of the cerebrum, classified as either fibrillary or protoplasmic, were operated on during the three year period. Relatively few patients lived for over five years, the average survival period being only thirty-five and eight-tenths months; only 1 patient in the entire series was apparently rid of the tumor and practically well. The same gloomy prospect for these patients is indicated by the data on the entire Cushing series of 164 cases. Only 14 patients were alive at the time of Eisenhardt's report, 1 of them having survived for twenty-one years. Five others, though dead when she collected her material, had nevertheless survived for from five to nine years.

Cerebellar.—The picture presented by histologically similar tumors located in the cerebellum, usually in children or young adults, is altogether different. There were 7 cases of this type in 1925-1926; 2 of the patients died as a result of the

operation. Of the remaining 5, a man aged 35, owing to circumstances at the time of operation, had merely decompression and biopsy and died fourteen months later. Another lived a useful life for eleven years and nine months after operation. The other 3 patients all underwent radical operative procedures and were alive and well from thirteen to fourteen years after the operation. Indeed, a patient who was nearly blind even recovered useful vision. Van Wagenen, whose series contained 11 cases of cerebellar astrocytoma, stated that in 8 of them the patient was still living, and Cairns made a similar report in 3 of 4 cases. Examination of the total number of cases of cerebellar astrocytoma for the three years, therefore, revealed that 15 of 22 patients were alive and well at the time of the surveys, seven to thirteen years after the operation, and experience with older cases in Dr. Cushing's series indicates that the prognosis for these survivors should continue to be good. Indeed, in a total of 91 cases in this series, 35 patients were alive and for the most part well in 1935, five to twenty-six years after operation, and 4 others, though dead at the time of this survey, had lived for from six to fifteen years.

In seeking an explanation for the obvious difference in the behavior of histologically similar tumors a number of factors must be taken into consideration. Undoubtedly the age of the patient and the location of the tumor are basically important constitutional factors. Another factor, however, is the greater freedom permissible to the surgeon in the radical extirpation of an infiltrating tumor of the cerebellum, the function of which can easily be sacrificed, as compared with his limitations when dealing with a tumor involving the motor or speech areas of the cerebrum. Even in the cases of cerebellar medulloblastoma, in which the intrinsic nature of the tumor is malignant, its complete surgical removal would be conceivable but for the fact that the stalk of the neoplasm appears characteristically to originate from the calamus scriptorius, from which, unfortunately, it cannot be widely excised.

OLIGODENDROGLIOMA

Only 3 cases of oligodendroglioma were encountered during the year under consideration. All were in the frontal region in adults. One patient died immediately after operation. A second, except for slight aphasia and right hemiparesis, was well for nearly four years. A second operation was then performed, and the patient remained stuporous and paralyzed for six months, until his death, four years and seven months after the first operation. The third patient was alive and well thirteen years after a radical operation, except for rare seizures, of which he has had none in the past four years, and poor vision in the left eye.

In 1924-1925 Van Wagenen observed 4 cases of oligodendroglioma, in all of which the location was also the frontal region. Although none of these patients were alive at the time of his investigation, they showed an average survival period of six years and two months. In the year (1927-1928) of Cairns's report, there were 2 cases of oligodendroglioma; 1 of the patients died one year and nine months and the other nine years after operation.

A total of 9 cases in three years suggests that the oligodendroglioma is relatively rare; the presence of most tumors of this type in the frontal region indicates that this area is a favorite location for the oligodendroglioma, and, although only 1 patient was still living more than ten years after operation, an average survival period of six years and four months tends to show that the tumor is relatively benign. The complete series contained also relatively few (27) cases of this tumor. The survivor previously mentioned was the only one alive at the time of Eisenhardt's report, although 5 had lived for from five to thirteen years after operation.

EPENDYMOMA

The present series contained 3 cases of tumors originating from ependymal cells. In 2 of these the tumor was located in the cerebellum and in 1 in the right cerebral hemisphere. All 3 of the patients were alive, and the 2 with cerebellar ependymoma were fairly well at the time of this investigation, ten to fourteen years, respectively, after operation. The patient with the tumor of the right cerebral hemisphere continued to be well for over ten years, and then showed signs of recurrence, for which a second operation was successfully performed by Dr. Gilbert Horrax.

Van Wagenen's series also contained 3 cases of this tumor, in all of which the growth was cerebral. Two of the patients were alive at the time of his survey, and the third had lived for four and one-half years after operation. During Cairns's year, an ependymoblastoma occurred in a patient who lived less than two years after operation.

Thus, of 7 patients with tumors of this type occurring in the three year period, 5 were still living, from seven to nearly fourteen years after operation, 1 died after four and one-half years and 1 after less than two years. The statistics for the entire series are not as favorable, for of 25 patients the only survivors in 1935 were apparently the same 5 persons who, four years later, when the present survey was made, were still alive. Two others were reported by Eisenhardt to have died after six and ten years, respectively.

SPONGIOBLASTOMA POLARE

Four patients with tumors of this variety were operated on during 1925-1926. One died immediately and another one month after operation. Of the remaining 2 patients, 1 was a child whose tumor, located in the cerebellum, was completely removed. She was alive and well thirteen years and one month after operation. The fourth patient was a child in whom the polar spongioblastoma originated from the optic chiasm. She reported that she was alive and well, except for impaired eyesight, thirteen years and one month after operation. Her vision at the time of operation was extremely poor, but it must have improved later, since she was able to finish high school and live a normal life.

Van Wagenen reported 1 case of "optic chiasm glioma," presumably a polar spongioblastoma, occurring in a patient who was still alive and teaching eight years after operation.

Cairns also reported 1 case of this tumor located in the vermis of the cerebellum. The patient was alive and well nine years after operation.

One sees again, therefore, in the spongioblastoma polare a tumor not only relatively benign, with slight tendency to recur after extirpation, but so sluggish in growth that, without its removal by surgical means, as in the cases in which it originated in the optic chiasm, its presence is often compatible with comfortable, even relatively healthy, existence. These conclusions were borne out by Eisenhardt, who in a total of 32 cases reported that 10 patients were living from five to fifteen years after operation, and that another had survived nine years after operation.

PAPILLOMA

Papilloma of the choroid plexus is rare. One case occurred in my series, in which two attempts were required for complete removal of the tumor from the fourth ventricle. The patient was alive and well, except for facial palsy, thirteen years after operation. Van Wagenen had no case, and Cairns had 1 case, in

which the patient was also living at the time of his study, over eight years after operation. The entire Cushing series contained only 12 cases of this tumor; 4 of the patients were living in 1935, from five to nine years after operation.

MISCELLANEOUS GLIOMAS

Three cases of atypical gliomas, in 1 of which the patient died after operation, and 5 cases of gliomas verified by examination of the cystic fluid alone occurred in 1925-1926. Of the 7 patients who survived operation, 1 was alive and well thirteen years after evacuation of a cyst of the cerebellum; the others had all died, after an average survival period of fourteen months.

ADENOMA OF THE PITUITARY GLAND

The year 1925-1926 was particularly rich in cases of pituitary adenoma. Thus, 11 patients with chromophilic tumors and associated acromegaly were operated on during this year, and 22 with chromophobic adenomas were similarly treated. One patient with chromophilic and 2 with chromophobic adenomas died as a result of the operation. This was the last full year in which the transphenoid operation was still in use and, with 1 exception, in which a transfrontal procedure was employed, the tumors in all cases were approached by this route.

Of the 10 patients with chromophilic adenoma, 7 were alive from ten to thirteen years after the operation. One had died five years and three months and another seven years and five months after the operation. A third patient died of extension of the tumor to the third ventricle twelve years and seven months after operation. Most of the patients had received roentgen radiation to supplement the surgical therapy. Naturally, once acromegalic always acromegalic, and although the patients with chromophilic adenomas were alive, most of them suffered from the disfigurement and other discomforts of acromegaly. In 2 patients, visual acuity failed several years after operation, in spite of irradiation. One patient experienced convulsive seizures, which were demonstrated by ventriculograms to be due to an intracranial extension of the tumor; this seemed to yield to further irradiation.

It is obvious that, even if mechanically possible, it would be undesirable to remove the entire tumor and thus deprive the patient completely of the function of the pituitary gland. On the other hand, the unextirpated portion, if it does not burn itself out or yield to control by irradiation, may continue to pour its secretions into the circulation, or even increase in volume to compress again the neighboring structures.

Of the 20 patients with chromophobic adenoma of the pituitary gland who survived the operation, only 8 were known to be alive ten to thirteen years after the operation, and 12 died from twenty-three months to twelve years and five months after the operation, the average period of survival being five years and two months. In 2 instances death was reported to result from "stroke"—evidently an apoplectic episode resulting in sudden unconsciousness and death, the occurrence of which Cairns also mentioned in his series.

Unfortunately, my colleagues did not consider separately the chromophilic and the chromophobic adenomas. In my series, however, it seemed definite that the patients with acromegaly survived longer and were, on the whole, in better health than the patients with chromophobic tumors. The statistics for Dr. Cushing's entire series are not sufficiently confirmatory on this point to justify much stress. There were, however, 264 cases of chromophobic adenomas, in 112 of which

(42 per cent) there was a survival period of five or more years, while in 39, or 53 per cent, of the 73 cases of chromophilic tumor there was an equal period of survival.

From a more detailed study of the same material Henderson.[8] concluded: "Chromophobe adenomata produce only local compression effects, whereas acidophile adenomata evoke general constitutional disturbances and often local effects in addition. The adenocarcinomata are apt to infiltrate surrounding structures . . .

"The late results, analysed on the basis of the duration of improvement after operation, indicate great variability in the rate of growth and behavior of the tumours. After a successful transphenoidal operation without irradiation some patients had no further trouble for as long as twenty years. On the other hand, a rapid recurrence within two or three years may take place even after a far more radical transfrontal operation plus X-ray treatment. While many patients maintained this improved status for ten to twenty years, 95 per cent of those who had a recurrence showed indications of it within five years after operation . . .

"The clinical course of [acidophil adenomata] differs from that of the chromophobe adenomata. The two types of symptoms—local pressure (visual) effects and system effects—frequently show spontaneous remissions and exacerbations, and often respond differently to treatment. Operation usually produces marked improvement in vision, but may have no effect on the severe headaches, especially in cases in which there is a small tumour. The systemic disturbances are ultimately apt to be the most serious because of the deleterious effects of the hormonal secretion on the cardiovascular system and on sugar metabolism. The operation mortality rate is slightly higher than for the chromophobe adenomata, but the late surgical results appear to be better. The acidophil tumours are more amenable to X-ray therapy."

There was a total of 88 cases of pituitary adenoma for the three years, in 56 of which the patients were alive from seven to eleven years after operation. Many of these, however, were suffering from poor vision, general asthenia, impotence, drowsiness and headaches.

MENINGIOMA

Eighteen patients with meningiomas were operated on during 1925-1926. Two of the patients died as a result of the operation. Of the remaining 16, 7 were living at the time of this survey, between twelve and thirteen years after operation. Three of these patients had a primary complaint of failing vision, and the tumor was located in the suprasellar region. The patients were all remarkably improved by the operation and remained well. In 2 instances the tumor was located in the sylvian region—in 1 on the right and in 1 on the left side. One of the patients had temporary hemiplegia after operation, from which he recovered completely. The other has continued to have occasional petit mal attacks and is taking phenobarbital steadily, but is otherwise well. In the sixth patient the tumor was located in the right frontal region. Visual acuity was markedly diminished before operation, and had not improved at the time of discharge from the hospital. Several years later, however, he reported that his left eye had recovered serviceable vision and that he was doing light work. The seventh patient had a tumor of the left

8. Henderson, W. R.: The Pituitary Adenomata: Follow-Up Study of Surgical Results in Three Hundred and Thirty-Eight Cases (Dr. Harvey Cushing's Series), Brit. J. Surg. **26**:809-921, 1939.

rolandic region and has been well since operation, for thirteen years. Two patients had tumors originating in the mesial aspect of the sphenoid ridge which could not be removed at operation; they died ten and seventh months, respectively, after unsuccessful attempts at removal. In 2 cases the tumor was located in the posterior fossa, anterior to the pons; the lesions could not be removed, and the patients died eight and six months, respectively, after unsuccessful operations. In this series were the celebrated cases of T. J. Donovan and Dorothy Russell, both of whom had malignant, rapidly recurrent lesions. The patients were operated on eleven and seventeen times, respectively, and died twelve years four months and thirteen years four months, respectively, after the initial procedure.

The seventh patient in this group was an elderly missionary from whose right frontal region a meningioma was completely extirpated. He was cured of his symptoms, but died suddenly of "heart failure" seven years and nine months after the operation.

Of the 2 remaining patients, 1 had a lesion located in the left parasagittal region, on which incomplete operation was performed, leaving a small amount of tumor attached to the longitudinal sinus. The patient was well for over eight years, when she showed signs of recurrence of tumor on the opposite side and died during an attempt to remove it at another hospital.

The last of the group was a young woman with a very large meningioma of the olfactory groove, whose symptoms were advanced and whose general condition was poor. Only partial extirpation of the tumor was possible. She left the hospital in poor condition, but improved slowly and felt fairly well for about one year, when she died at home, eighteen months after operation.

It is evident from the foregoing data that the meningioma series, for the year under discussion, formed an instructive group, exemplifying by means of the 18 cases almost every problem arising in connection with this tumor. While meningiomas are generally considered benign, the cases of Donovan and Russell have shown that these tumors can be locally malignant, as indicated by their rapid regrowth. Even when histologically benign, however, the location, as in the posterior fossa anterior to the pons or in the middle fossa adjacent to the midline, may make them surgically irremovable. Again, even when the region is approachable, if the tumor is attached to such an important structure as the superior longitudinal sinus, especially posterior to its anterior third, complete removal may be impossible and recurrence may take place at some later date. Occasionally the advanced stage of the disease, as in the case of the large tumor of the olfactory groove, militates against a surgical cure. Even when the tumor is completely removed the patient may be of such advanced years at the time of operation that the postoperative period of survival is interrupted by death from "natural" causes.

As to surgical cure, the data here presented indicate that the suprasellar meningiomas, if the damage to the optic nerves and chiasm is not already irreparable, are the ones which can be completely removed without disagreeable sequelae. Next to these in favorable prognosis are the tumors originating over the convexities of the brain, the removal of which presents relatively few surgical difficulties. However, owing either to the softening of the compressed brain tissue in the tumor bed or the damage to this tissue at the time of the operation, hemiplegias or convulsive seizures may result.

Van Wagenen reported 16 cases of meningiomas, 4 of which were suprasellar. Three patients recovered from visual disturbance after operation, but vision of the fourth, who was nearly blind before operation, was not improved. Three of

the patients were still alive at the time of the study, from seven to eight years after operation. In the other 12 cases Van Wagenen classified the meningioma as "associated with the convexity of the cerebrum," without further distinction. Five of the patients were still living when he made his report. Four of them considered themselves as "well," but the fifth, who had had hemiplegia before operation, did not show improvement with respect to this disability. The average survival period for his entire series of patients, both living and dead, was six years four and a half months. Cairns reported on 31 cases during his year of service; 5 of the patients died immediately after operation and 8 others at varying intervals afterward. Eighteen patients had survived for seven to nine years at the time of his survey. Eight of the survivors were well and working. Six were working but had major symptoms. The remaining 4 were too sick to work.

In summary, there was a total of 65 cases of meningioma in the three years from 1924 to 1927. Thirty-two of the patients were alive at the time of the three separate reports, from seven to thirteen years after operation was performed. Twenty-five of them were essentially well or suffering from symptoms that did not incapacitate them from work, while 7 were invalids.

The total Cushing series[9] contained 271 cases of meningiomas. In 119 of these, the patients survived five or more years, and in 92 instances they were still alive in 1935, from five to twenty-five years after operation.

ACOUSTIC NEURINOMA

In the twelve months between Oct. 1, 1925 and Oct. 1, 1926, Dr. Cushing operated on 19 patients with neurinomas located in the cerebellopontile angle, originating from the acoustic nerve. Two patients died after operation, and 1 was not heard from after leaving the hospital. Of the remaining 16 patients, 9 were still living at the time of this survey, from thirteen to nineteen years after the first operation. Seven patients had died from fifteen months to ten years and two months after operation, with an average period of survival of four years and three months.

The acoustic neurinoma is a benign tumor, but, because of its location, is responsible for a series of debilitating symptoms, and eventually death. Its surgical removal, again because of its location, is attended with serious risks to the health and life of the victim. If, however, the exigencies of a given case permit its complete, or nearly complete, removal, without too much damage to neighboring nerves or too much hemorrhage from the neighboring blood vessels, the patient may be permanently cured or relieved for a long period. A closer examination of the cases in the present series confirms this point of view. With the guidance of the surgeon's impression, as revealed in his notes dictated immediately after each operation, the procedures in these cases may be divided into: (1) exploration, with or without biopsy of the tumor; (2) partial removal of the tumor; (3) radical but incomplete extirpation; (4) subtotal removal, and (5) total removal. A number of the patients were operated on twice, or even three times. It will be noted from table 4 that the patients who are still alive or those who died after a long period of survival were the patients who either at the first or at an eventual operation were treated by the most radical surgical procedures. It requires little proof to substantiate the claim that a benign tumor completely and successfully removed results in cure

9. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behaviour, Life History, and Surgical End Results, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

of the disease. But the data reveal what seems to be a new aspect of this problem, namely, that, short of total extirpation, the degree of improvement and the duration of life after operation vary directly with the amount of tumor that has been removed (table 4).

Of the 7 patients who had already died at the time of this study, useful life was vouchsafed to a number for varying periods before death. One was a physician who returned to his practice for ten years, when he died of cardiorenal disease. Two women each gave birth to a child and lived comfortably until from six to twelve months before death, for three and one-half to seven and one-half years,

TABLE 4.—*Acoustic Neurinoma: Survival Period in Relation to Type of Operation*

Case	Number of Operations	Type of Operation	Survival After First Operation
1	1	Partial	1 year 3 months
2	2	(1) Partial (2) Partial	1 year 5 months
3	1	Partial	2 years 6 months
4	2	(1) Partial (2) Partial	3 years 1 month
5	1	Partial	3 years 7 months
6	1	Subtotal	7 years 6 months
7	1	Subtotal	10 years 2 months (death from cardiorenal disease)
8	3	(1) Partial (2) Radical (3) Total	Still living (13 years 9 months)
9	3	(1) Exploration (2) Radical (3) Radical	Still living (13 years 4 months)
10	1	Subtotal	Still living (13 years)
11	1	Radical	Still living (13 years 3 months)
12	1	Subtotal	Still living (13 years)
13	2	(1) Exploration with biopsy (2) Radical	Still living (13 years 3 months)
14	3	(1) Exploration (2) Radical (3) Radical	Still living (19 years 6 months)
15	2	(1) Partial (2) Subtotal	Still living (13 years 4 months)
16	2	(1) Radical (2) Total	Still living (13 years 6 months)

respectively. One man was well after a first operation, but suffered so much after a second that he shot himself nine months later, or three years and one month after the first procedure. Two patients gained no relief from an operation, after which they died in fifteen and seventeen months, respectively. Of the 9 living patients, 3 report that they are entirely well. One is blind but otherwise well. Four have disturbances of the cranial nerves but are able to "carry on." The ninth reports that he is "unable to do anything of a practical nature, but each day takes an hour or two of exercise."

In 1924-1925, 11 patients were operated on for removal of this tumor, of whom 7 were living and 4 had died at the time of the report. In 1926-1927 10 patients were operated on, 8 of whom survived.

The three year period thus included 40 cases of acoustic neurinoma, in 24 of which the patients were still living seven to eleven years after the operation. Of

this number, however, only about 10 were well enough to perform their full work, the others suffering all degrees of disability from partial handicaps to complete invalidism. In 176 of the complete series of 2,000 cases, there were tumors of this type; in 77 instances the patients survived five or more years after the operation.

The modern tendency is undoubtedly in the direction of increasingly radical operative treatment of these tumors,[10] and the operative procedures have been modified at most clinics since the one advocated by Dr. Cushing in 1917. However, the data here presented seem to indicate that there is little difference in the period of survival between the patients who have total and those who have subtotal extirpation of the tumor. This is important in that, occasionally, in striving for the last bit of tissue to make the extirpation complete one may cause irreparable damage to the medulla or cranial nerves.

CRANIOPHARYNGIOMA

Like the acoustic neurinoma, the craniopharyngioma, usually a partly cystic, congenital tumor, is benign, but because of its location presents almost insurmountable problems in its surgical removal. Consequently, the operative mortality is high if a radical procedure is undertaken, and frequently the patients who survive suffer from profound disturbances of fat and water metabolism, autonomic functions and the sleep mechanism. On the other hand, simple evacuation of the cyst, while much less dangerous a procedure, usually is followed by relatively rapid recurrence of symptoms.

There were 12 cases of this tumor in this series, in 2 of which the patients died immediately after operation. Of the remaining 10 patients, only 2 were still living thirteen years and ten months and thirteen years, respectively, after operation. One of these was a midget, who also suffered from diabetes insipidus. The other was a young man who reported that he was "quite well" eleven years after operation, which was performed when he was 12 years of age and consisted of evacuation of the cyst and partial removal of the solid portion of the tumor. However, a report from Dr. Loyal Davis, of Chicago, who saw him at about the time of this investigation, stated: "Thirst still is excessive, but is spasmodic during the day. For example, he starts the day with three or four glasses of water, eats many oranges throughout the day and drinks three glasses of liquid in the evening. He voids a large quantity of urine once during the night, usually about 4 o'clock in the morning. Incontinence is rare, but does occur. He has not been taking solution of posterior pituitary for some time. He complains of headaches which occur daily, and I find that he has been in the habit of taking an alkaline proprietary product, once or twice a day, with some relief.

"He is 65 inches [165 cm.] tall, and at present his blood pressure is 92 systolic and 66 diastolic. His pulse rate is 64 and his temperature 98.6 F. His metabolic rate is —28 per cent, with a pulse rate of 56, and his weight is 127.5 pounds [57.8 Kg.]. The red blood cell count is 5,600,000; the white cell count 12,200, and the hemoglobin content 14.89 Gm."

Of the 8 patients with craniopharyngioma who died, the average period of survival was only 23 months; almost all of them were nearly or completely disabled during this period.

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10. Horrax, G., and Poppin, J. L.: Experience with the Total and Intracapsular Extirpation of Acoustic Neuromata, Ann. Surg. **110**:513-524, 1939.

Van Wagenen reported 6 cases, in 1 of which the patient was also alive and well eight years after operation. The other 5 had an average survival period of seventeen months and an average period of usefulness of twelve months. Cairns's series, although not reported in detail, included 5 cases, in 1 of which also a single patient survived. In summary, the three year block thus included 23 cases of craniopharyngioma, in only 4 of which the patients were living at the time of the investigation and moderately well; the others were but little benefited during a short period of survival. The results of Dr. Cushing's thirty years' experience yielded 92 cases, in only 24 of which the patients survived five or more years—data which bear out the preceding evidence.

By extirpation of part of one frontal lobe, section of one optic nerve or the optic chiasm and other means of enlarging the exposure at operation, radical procedures are again finding favor. However, the fact remains that when a craniopharyngioma is adherent to the neighboring hypothalamus operation under the most favorable circumstances is bound to result in damage to this important structure. A glimmer of hope is visible in the experience of the group in Philadelphia with roentgen treatment of these lesions following evacuation of the cyst.[11] Contrary to the preconceived notion that tumors consisting of adult tissue, such as the craniopharyngiomas, cannot be expected to respond to irradiation, experience has shown that radiation appears to have an inhibitory effect on the reaccumulation of cystic fluid, and the patients do well after the treatment. The results with 3 patients whom I treated in this way bear out the experience of Dr. Frazier and his co-workers.

METASTATIC CARCINOMA

Five patients were operated on during the twelve month period. Four of them died before leaving the hospital. The fifth survived five months. Van Wagenen reported on 4 cases in which the patients survived for an average of thirteen months, with an average useful life of three months. Cairns's series included 8 cases, in 1 of which the patient died before leaving the hospital and in 5 others within five months. Two patients lived for more than two years. One of them lived a useful life for six months, and the second returned to work as a train driver for fifteen months. Generally, then, the outlook for patients with metastatic carcinoma of the brain is one of short survival, whether operation for the intracranial metastasis is undertaken or not. In only 1 of 85 cases in which Dr. Cushing performed operation during a period of thirty years did the patient live as long as five years after operation. Carcinoma of the brain is hopeless, but in the occasional case of a single large metastatic tumor improvement sufficient to warrant the operation may occur.

SUMMARY

The late results (after from thirteen to fourteen years or more) in 152 verified cases of tumor of the brain in which Dr. Cushing performed operation in 1925-1926 are reported. Twenty-three of the patients died before leaving the hospital. Eighty-one died in from a few months to seventeen years after the first operation. Forty-five were alive and most

11. Carpentier, R. C.; Chamberlin, G. W., and Frazier, C. H.: The Treatment of Hypophyseal Stalk Tumors by Evacuation and Irradiation, Am. J. Roentgenol. **38**:162-177, 1937.

of them well, at the time of this survey, from thirteen to more than fourteen years after operation.

The results of the work for the year 1925-1926 (my year as resident in Dr. Cushing's service) are compared with those reported by Van Wagenen for the year immediately preceding (1924-1925) and by Cairns for the year immediately following (1926-1927).

A total of 457 cases are thus reviewed, in 287 of which the patients had died and in 170 of which the patients were still living at the time the three studies were made, from seven to fourteen years after operation.

In table 1 the ultimate results for the individual types of tumors are indicated.

The general impression is gained that improvement in the future treatment of tumors of the brain must take two directions: in the case of benign tumors, technical improvement to make surgical removal more complete and less hazardous; and in the case of malignant tumors, some form of therapy other than surgical.

Case Reports

AN UNCLASSIFIED DEGENERATIVE DISEASE OF THE CENTRAL NERVOUS SYSTEM

W. J. C. Verhaart, M.D., Batavia, Java, Netherland East Indies

In a recent paper [1] on ophthalmoneuromyelitis and multiple and diffuse sclerosis in natives and Chinese in the Netherland East Indies, I described a case of multiple sclerosis occurring in a Sundanese native, who for about ten years showed symptoms of spasticity and cerebellar ataxia (case 4, pages 104-105). The subject of this description has since died, and the postmortem examination revealed an entirely different disease than the suspected sclerosis. Thus far I have been unable to find a similar case in the literature, and although several years have passed since the patient's death no other case has come under my observation. Moreover, during 1938-1939 I had the opportunity to ask several outstanding neuropathologists in the Netherlands and in the United States about this case; none of them had encountered a similar one.

REPORT OF A CASE

History.—A Sundanese native Mamud was admitted to the general civil hospital at Batavia, Java, on May 14, 1931, at the age of about 40. For five years he had suffered from weakness of the legs and back and for the last two years walking had become impossible. Speech had become blurred during the same period. He had previously been well. There was no fever during the present illness.

Examination.—Neurologic examination on May 19 revealed: horizontal nystagmus; irregular and dysarthric speech; hyperactivity of deep reflexes in both arms and legs; some increase in muscular tonus; slight muscular power, and muscular atrophy. All movements were slow and ataxic; the plantar reflexes were distinctly dorsiflexor in type; the abdominal reflexes could not be elicited; sensibility was unimpaired.

The mental state showed no change; there was no dementia, but apathy was rather pronounced; spontaneous movements and psychic activity were both slight.

The report from the department of ophthalmology was papilla alba with central retinitis of long standing in the right eye; the left eye presented papilla albicans. Vision was 5/30 in the right eye and 5/50 in the left eye; correction could not be made. The Wassermann and Sachs-Georgi reactions of the blood and cerebrospinal fluid were negative. The spinal fluid contained 2 cells per cubic millimeter, and Nonne's reaction was slightly positive.

Course.—On July 21, 1931, Prof. van Wulfften Palthe found typical cerebellar ataxia of both the limbs and the trunk, Babinski's asynergia being demonstrable. Hypermetria and adiadokokinesia were present; speech was slow and monotonous; horizontal nystagmus and impairment of upward ocular movements were present. The deep reflexes were hyperactive; the abdominal reflexes could be elicited only

From the Department of Neuropathology, School of Medicine.

1. Verhaart, W. J. C.: Ophthalmo-Neuromyelitis, Multiple und diffuse Sklerose bei Ost-Asiaten in Niederländisch Ost-Indien, Acta psychiat. et neurol. **13**:93-122, 1938.

in the upper quadrants of both sides; the cremaster reflexes were diminished; intention tremor was slight.

The patient was last examined in January 1935. At that time all movements had become still more slow and awkward; a coarse tremor accompanied them; the ocular movements were greatly impaired in all directions; the masseter muscles were atrophic; horizontal and vertical nystagmus were associated with ocular movements. Facial motility was weak on both sides; the tongue deviated to the left when protruded, and its motility was severely impaired; the jaw deviated to

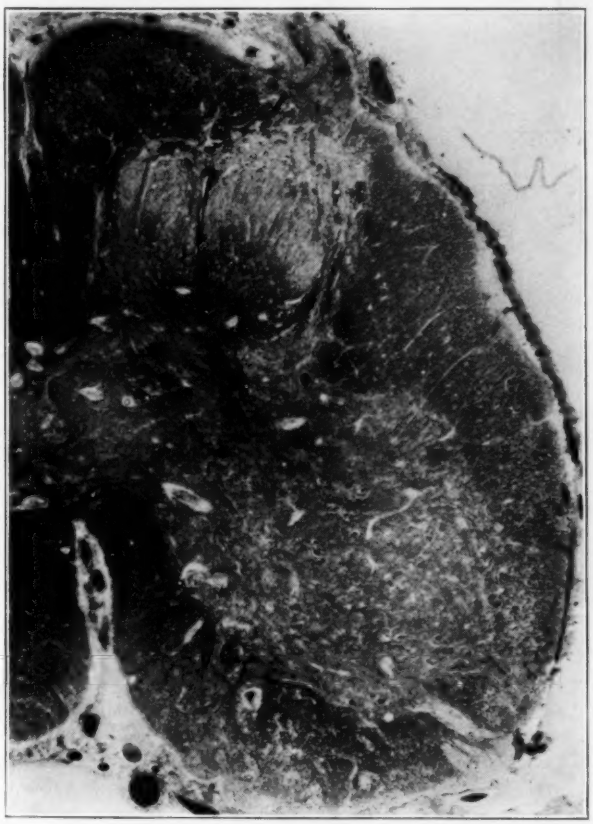

Fig. 1.—Section from a lumbar segment of the cord. The anterior horn shows preservation of eleven motor ganglion cells.

This photograph and those in the accompanying figures were made from Weigert-Pal sections counterstained with Grenacher's carmine solution. The sections have a thickness of 30 microns.

the right when the mouth was opened wide. Speech was dysarthric, slow, monotonous and weak. The tendon reflexes were hyperactive, except the ankle jerks, which were not elicited; the plantar reflexes were dorsiflexor in type. The mental state was still unimpaired; the mood was generally quiet and contented; orientation was correct.

In February 1935 the patient was transferred to a hospital for chronic invalids, where he died in June.

Summary of Clinical Data.—A Sundanese native aged 35 showed gradual development of general muscular weakness, cerebellar ataxia and speech disturbances,

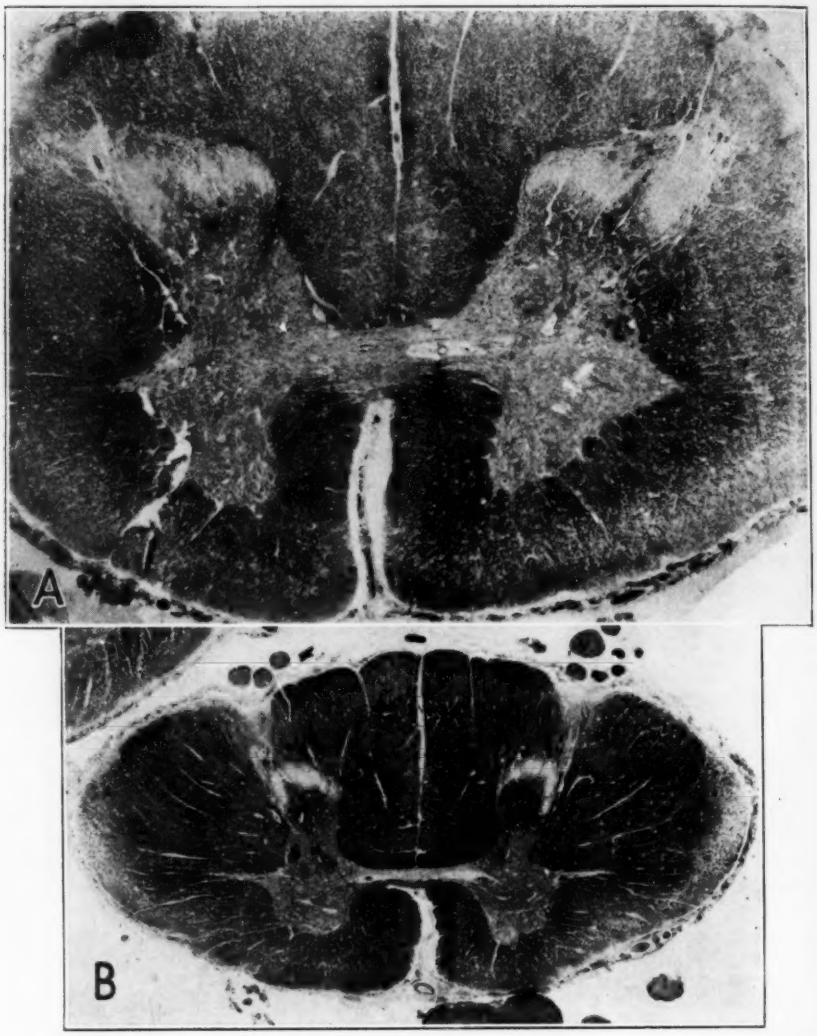

Fig. 2.—*A*, section from the twelfth thoracic segment (lower magnification than that in figure 1). The anterior horn and Clarke's column are almost devoid of ganglion cells.

B, section from a higher dorsal segment than that in *A*. Demyelination is obvious in the area of the spinocerebellar tracts, and is somewhat apparent in Goll's column.

without fever. After five years of illness nystagmus, impairment of ocular movements, hyperactivity of tendon reflexes, diminution of abdominal reflexes and a bilateral Babinski response were found. Four years later, shortly before his death, the ankle jerks had disappeared, ocular movements were far more severely impaired and the fifth, seventh and twelfth cranial nerves showed motor weakness. The case was regarded as one of a slowly progressive form of multiple sclerosis.

Autopsy (Dr. Soewadji).—There were lobar pneumonia and some ascites, but no cirrhosis of the liver. Macroscopically, the brain showed slight atrophy of the pons, cerebellum and medulla. The lateral ventricles were somewhat distended; the basal arteries were normal.

Histologic Examination.—Study of the cerebral cortex revealed slight paucity of ganglion cells everywhere, involving all layers. The small vessels were somewhat fibrotic; in the putamen and globus pallidus were a number of softenings of various sizes; the cortex showed only small perivascular lacunas. No changes were observed in the cerebellar cortex; the Purkinje cells were numerous; the granular and molecular layers were unchanged; the dentate nucleus alone had lost about one-half its neurons, and the neuroglia cells within this nucleus were somewhat increased in size and number. The frontal half of the globus pallidus showed softenings similar to those of the putamen; the ganglion cells were normal.

Severe changes were present in the spinal cord, medulla, pons and mesencephalon, and were predominant in the corpus subthalamicus and the caudal half of the globus pallidus. In the cord, the ganglion cells of the anterior horn had almost disappeared, a few only being preserved (fig. 1). There was no noticeable difference between the upper and the lower segments. In the dorsal segments, the neurons of Clarke's column had also disappeared (fig. 2*A*); the number of cells of the posterior horn was less decreased. The preserved neurons were of relatively normal appearance; Nissl bodies were still visible, but some showed too large a quantity of lipochrome. The glial reaction consisted only of slight proliferation of astrocytes and slight anisomorphic gliosis.

As a result of this severe degeneration of ganglion cells, distinct demyelination was present in the anterior commissure, the anterior roots and the spinocerebellar tracts. Hence, in the upper thoracic segments the anterolateral margin of the cord appeared very pale in sections stained by the Weigert-Pal method (fig. 23). The column of Goll was also somewhat demyelinated; the other spinal fiber systems, however, especially the pyramidal and anterior columns, were not damaged.

In the medulla, similar damage was present. The nuclei of the motor nerves had almost completely lost their neurons. The nucleus of the twelfth nerve (fig. 3*A*) and the nuclei of the abducens, trochlear and oculomotor nerves (fig. 3*B*) were almost completely devoid of large motor ganglion cells. The motor nuclei of the tenth, seventh and fifth nerves contained a somewhat larger number of ganglion cells which had escaped degeneration; these were estimated to constitute about one third of the total number. The motor roots were rare and in most slides could hardly be found.

The tegmentum medullae was somewhat decreased; the olives and the olivocerebellar system were undamaged; the restiform body showed demyelination in the lateral area, where the dorsal spinocerebellar tract had disappeared. In von Monakow's triangular field, dorsolateral to the interior olive, demyelination was also conspicuous (fig. 4), owing to degeneration of the spinocerebellar tracts, and perhaps the spinothalamic tract.

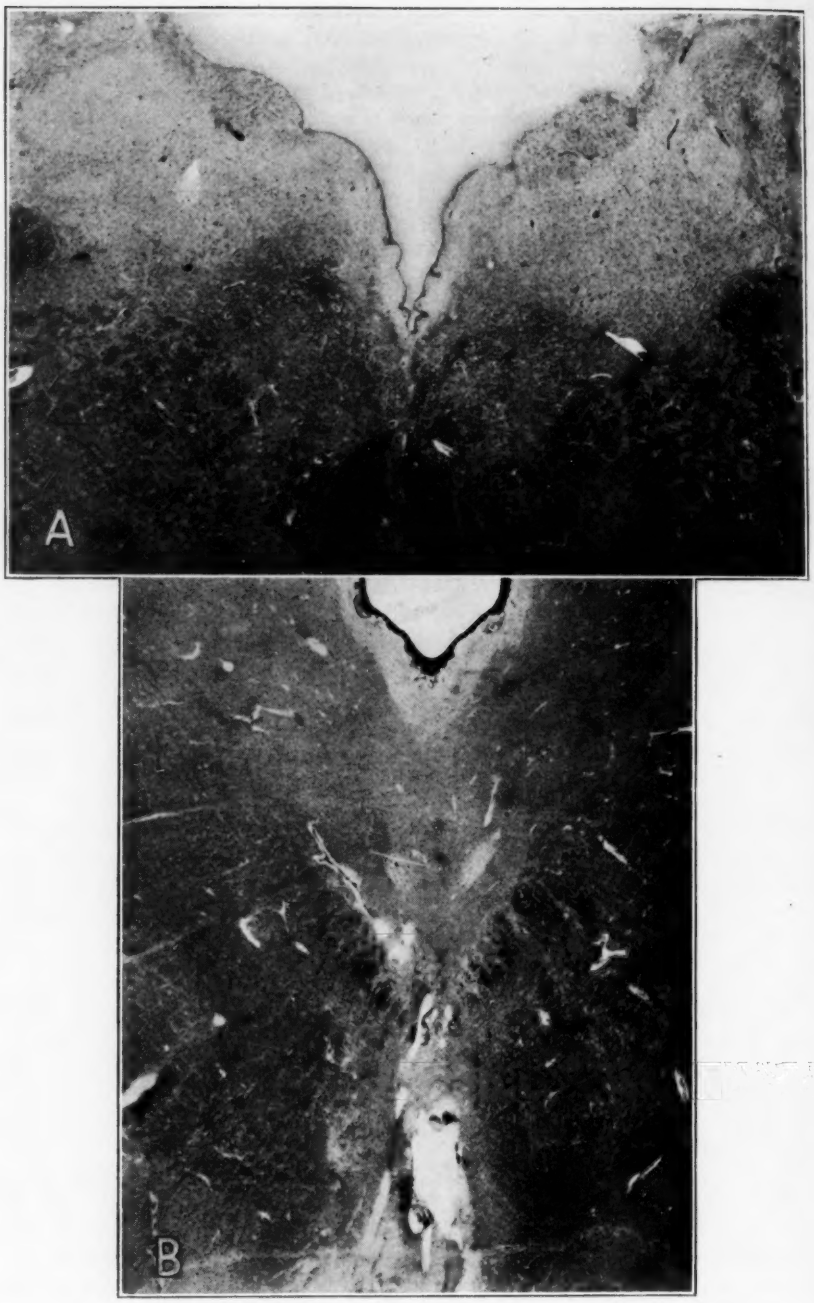

Fig. 3.—*A*, section showing the nucleus of the hypoglossal nerve almost devoid of neurons, five or six being visible. *B*, section showing the nucleus of the oculomotor nerve almost wholly degenerated, the motor roots having disappeared also.

In the pons the basal nuclei were somewhat atrophic, those situated between the bundles of the pyramidal tract showing special paucity of ganglion cells. The middle cerebellar peduncle, as well as the middle longitudinal fasciculus, both lemnisci and the central tegmental tract, showed no loss of myelination; the sensory nuclei were unchanged.

In the reticular tegmental nuclei of the pons and mesencephalon a number of ganglion cells were present; however, the moderate proliferation of astrocytes may be interpreted as a reaction to partial degeneration of the ganglion cells. In the superior colliculus the tissue was somewhat spongy and contained a number of proliferated astrocytes.

In the dentate nucleus, about one-half the neurons had disappeared; the superior peduncle and the hilus were poorly provided with myelinated fibers.

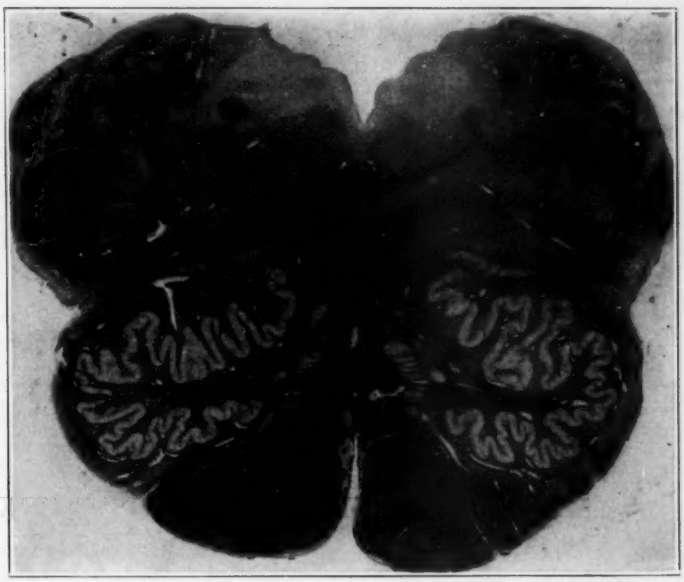

Fig. 4.—Medulla at the middle of the inferior olive. In von Monakow's triangular field pronounced demyelination is present, owing to degeneration of the spinocerebellar tracts. The hypoglossal nerves are poorly provided with myelinated fibers; the motor roots are absent.

The most severe atrophy and degeneration were observed in the subthalamic body of Luys, which had lost about two thirds of its volume (fig. 5). In the remaining part the neurons were rare and the glia nuclei numerous. The dorsal capsule was severely demyelinated; the pallidosubthalamic connections, such as Edinger's *Kammsystem* and even Forel's field H_2, were greatly degenerated. In the caudal half of the globus pallidus similar, though somewhat less severe, degeneration was present, the neurons being sparse and the thick pallidofugal fiber systems smaller and less myelinated. The laterofrontal part of the substantia nigra, the part directly connected with the pallidum and the subthalamic body, had also lost a number of neurons, but other parts of the substantia nigra were undamaged.

Nowhere in the central nervous system were there any signs of inflammation; scavenger cells, clusters of glia cells and perivascular demyelination were nowhere present; the preserved ganglion cells in the damaged centers were not swollen or laden with products of abnormal metabolism; glial reaction was nonspecific and slight; abnormal neuroglia cells were absent.

Summary of Pathologic Data.—In this case extensive and severe degeneration of ganglion cells was observed in all the motor nuclei; the anterior horns of the cord and the motor nuclei of the cranial nerves were equally attacked. Clarke's column also had lost all its neurons; the posterior horns showed moderate degeneration of ganglion cells. In the brain stem, the reticular nuclei, the basal pontile nuclei and the superior colliculus had lost some ganglion cells and showed aniso-

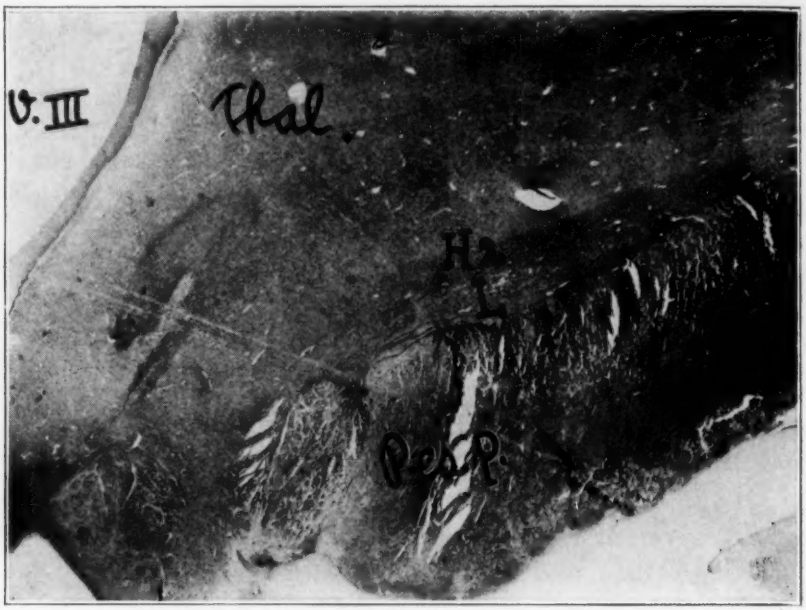

Fig. 5.—Section at the level of the greatest extent of Luys's body, demonstrating the immense atrophy of the corpus subthalamicus and Forel's tract H_2. H_2 indicates Forel's tract H_2; *L*, the corpus subthalamicus; *pes. p.*, the pes pedunculi; *thal.*, the thalamus, and *V. III*, the third ventricle.

morphic gliosis of moderate degree. Most severely damaged, however, were the corpus subthalamicus, the caudal part of the globus pallidus and the frontolateral cell group of the substantia nigra. The dentate nucleus showed moderate loss of neurons. The cerebral cortex presented a scattered loss of neurons.

COMMENT

It is difficult to classify the disease in this case. It may be compared with a number of well established degenerative diseases of the central nervous system, but it differs from all of them in one or another characteristic feature.

Westphal-Strümpell pseudosclerosis clinically has many points in common with this condition, but such extensive degeneration of ganglion cells has not been found in cases of the former disease. Moreover, the typical Alzheimer glia cells of pseudosclerosis were lacking in this case.

In amyotrophic lateral sclerosis similar degeneration of motor neurons in the cord may occur, but the pyramidal tracts and motor cortex are also involved; the basal ganglia and subthalamic body, however, are undamaged. An atypical case of amyotrophic lateral sclerosis, having more in common with my case, was described by Teichmann.[2]

A few more or less similar cases of uncommon degenerative diseases, resembling well known types have been described by Hallervorden.[3] In one case the disease resembled Creutzfeld-Jakob spastic pseudosclerosis and in another olivopontocerebellar atrophy, but none of them was typical, as in each case some outstanding feature was lacking. Whether such variations are due to different etiologic factors or to a difference in the constitution of the subject (in my case perhaps the race of the patient) cannot as yet be determined. Perhaps the different endogenous and exogenous circumstances of the natives of Java may have some influence; Radsma[4] established that the acid-alkali balance, the hemoglobin and the lipoid content of the blood of natives and of Europeans in this country differ markedly. It is possible that these differences influence the metabolism of ganglion cells and their liability to certain types of degeneration.

Concerning the clinical symptoms, postmortem observations and clinical diagnosis, some final remarks are appropriate. It is obvious that in the present case the diagnosis could not have been made during life because a similar case was unknown. The condition resembled multiple sclerosis, especially at the onset; later, however, the progressive muscular weakness and atrophy should have suggested caution in diagnosis. The diagnosis of pseudosclerosis might seem more satisfactory, but the pronounced cerebellar symptoms made it more improbable than that of multiple sclerosis.

Most of the symptoms during life were in accord with the postmortem observations. The disease started with spasticity and cerebellar ataxia, due to lesions of the pallidosubthalamiconigral system and of the spinocerebellar tracts and dentate nucleus, respectively. Later flaccidity prevailed, because of the progressive degeneration of motor ganglion cells, which made spasticity impossible. From the clinical course it cannot be concluded that the lesions of the pallidosubthalamiconigral system and spinocerebellar tracts preceded those of the motor cells, because moderate degeneration of both may cause extrapyramidal spasticity, while with a severe lesion flaccidity and

2. Teichmann, E.: Ueber einem der amyotrophischen Lateralsclerose nahestehenden Krankheitsprozess mit psychischen Symptomen, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:32-44, 1937.

3. Hallervorden, J.: Eigenartige und nicht rubrizierbare Prozesse, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pp. 1085-1093.

4. Radsma, W.: Certain Physiologic Differences (Acid-Base Equilibrium and Blood Composition) Between European and Native Population Groups in Batavia, Nederl. tijdschr. v. geneesk. **79**:3066-3084, 1935.

muscular atrophy become paramount. The Babinski response, however, is unexplained by the postmortem observations. Neither the pyramidal tract anywhere in its course nor the anterior central convolution showed distinct degeneration or atrophy. Can this classic sign of a pyramidal lesion be due to a lesion elsewhere?

SUMMARY

The case is described of a Sundanese native aged 45 who had a progressive spastic-cerebellar-ataxic motor deficiency, of about ten years' duration, which in the later years of his illness changed to muscular weakness, flaccidity and muscular atrophy, involving the whole body.

Post mortem, there were observed severe degeneration of ganglion cells of the anterior horns of the cord, the motor nuclei of the brain stem, Clarke's column, the pallidosubthalamiconigral system, the basal pontile nuclei and the dentate nucleus. There was no swelling of ganglion cells, inflammation, primary demyelination, formation of abnormal glia cells or signs of abnormal metabolism in the central nervous system.

This case is compared with those of other atypical degenerative diseases that have been described in small numbers in the literature. No etiologic agent could be established.

INNERVATION COMPLEX OF THE LID AND JAW

L. Halpern, M.D., Jerusalem, Palestine

Under pathologic conditions one occasionally meets correlations of innervation which are not encountered under normal conditions. These correlations are frequently seen in the eye, especially the lid. I [1] have previously described two such phenomena affecting the movements of the lids. One phenomenon—a consensual retina-lid reflex—constitutes a sensorimotor correlation and consists of raising the lower lid when light is flashed into the opposite eye. The second phenomenon is purely motor, and is manifested by spastic closure of the lid on the side toward which the eyes are moved. Here, a further motor correlation involving the lid and jaw will be described.

C. N., a woman aged 65, has suffered for the last two years from involuntary opening and closing of the mouth. These movements have increased in frequency; during the last six months they have continued uninterruptedly, the patient being unable to do anything to stop them.

Examination showed that the nervous system was normal except for the automatic opening and closing of the mouth; simultaneously with this the tongue was pushed out and the lips were licked. These compulsory movements were made at the rate of 30 to 40 per minute and continued without interruption during the whole day, ceasing only with the advent of sleep.

This is a case of rhythmic hyperkinesis in an elderly woman, bearing all the signs of a functional complex involving the movements of chewing and champing. This particular form of extrapyramidal hyperkinesis is not unknown in advanced age. I have observed hyperkinesis of this type in an old man suffering from chorea senilis. This hyperkinetic complex has also been noted in postencephalitic patients.

The phenomenon observed in the case reported was as follows: When the patient was asked to close her eye the involuntary chewing and champing movements immediately ceased. The compulsory movements were in abeyance as long as the eyes remained closed, and were promptly resumed when the eyes were opened. The phenomenon could be observed at all times and remained unaltered at every examination.

Further examination showed: (1) that the disappearance of the hyperkinesis on closure of the lid was due to a simple motor correlation, and was unrelated to vision or an optical factor, for it did not occur when a shade was put over the eye and the lids were not closed; (2) that this motor correlation is connected with the volitional closure of the lid, since it did not occur when the lid was passively closed; (3)

From the Neurological Service of the Mayer de Rothschild Hadassah University Hospital.

1. Halpern, L.: Pathologische Correlationen am Bewegungsapparat des Auges, Confinia neurol. **1**:362, 1938.

that the effect of volitional closure involved only the lids, because similar innervation of other muscle groups, such as closing the fist or squeezing the hand, had no effect on the hyperkinesis. A change in the position of the head, the limbs or the body was also without effect. These facts point to the specific character of this motor correlation.

From the neurologic and ophthalmologic literature at my disposal, it appears that no observations on such a correlated effect of the movement of the lids on that of the jaw have been reported. The relationship between lid and jaw previously observed was of an opposite nature, namely, the movement of the lid and jaw in the Gunn phenomenon. This was first described in 1883 as "jaw-winking," and consists of raising the ptosed lids when the jaw performs chewing movements. The phenomenon herein described establishes the principle that the motor correlation between lid and jaw is of reciprocal and not one-sided nature.

The nerve relationships underlying this correlation may be considered. The underlying feature of the phenomenon is a chewing hyperkinesis. From the point of view of peripheral innervation, this hyperkinesis is brought about by the muscles moved in lowering the jaw—the mylohyoid and the anterior belly of the digastric—and those concerned in raising the jaw—the masseter and the temporal. The nerves involved are the motor part of the third division of the trigeminal nerve, supplying the muscles for chewing, and the hypoglossal nerve, concerned in the smacking movements of the tongue. The fact, however, that this hyperkinesis appears to be a functional entity occurring normally justifies the assumption of a movement complex under supranuclear control. The marked automatism and the regular periodicity of the hyperkinesis, which, in spite of the morphologic structure of the muscle, give it the character of a "vegetative" movement, as well as the disappearance of the hyperkinesis in sleep, confirm the view that this movement complex is not of cortical origin but derives from the basal ganglia. The stimulus factor in the phenomenon is provided by closure of the lid, which interrupts the chewing hyperkinesis. In view of its volitional character, the closure of the lid proves that one is dealing here with the effect of a central impulse on the facial nerve supplying the orbicularis oculi muscle. There is here, therefore, correlation between a cortical innervation of a cerebral nerve, in the role of an inductive factor, and a subcortical motor innervation controlling a movement complex as an induced result.

In the reverse circumstance, as in Gunn's phenomenon, in which the act of chewing appears as the inductive factor, the basic feature is the raising of the ptosed lid when the jaw performs the movements of chewing and eating. The factor usually considered to be involved here is a peripheral communication between the portion of the oculomotor nerve innervating the levator palpebrae muscle and the motor part of the trigeminal nerve, the volitional nature of the chewing movements being overlooked. Unlike the hyperkinesis of the new phenomenon, one is dealing in this instance with a central innervation of the chewing movements originating in a chewing center in the cortex. The correlation here is rather between a cortical motor innervation controlling a movement complex and the nuclear innervation of a cerebral nerve.

In this instance, unlike my case, the cerebral nerve constitutes the induced sphere and the movement complex the inductive factor.

An analysis and comparison of these innervation relationships show that all the nerves and nerve centers concerned play a part in the correlation between lid and jaw. One finds here the oculomotor nerve acting at the nuclear level and, at the cortical level, the facial nerve acting on the lid and the trigeminal nerve concerned in the motor innervation of the act of chewing. In this way, the innervation of the act of chewing is seemingly controlled by the corpus striatum, either through a chewing center in the cortex, as in Gunn's phenomenon, or through an automatic hyperkinesis, as in my case. The assumption of a somatotopographic arrangement of the basal ganglia in accordance with motor function is steadily gaining ground. Under these circumstances it appears justifiable to assume an innervation complex of lid and jaw.

This complex was observed under the pathologic conditions described. However, the opinion expressed by Goldstein [2] that the induced phenomena observed by him are rooted in the normal human being applies equally to the lid and jaw complex. This is borne out by the occasional appearance of Gunn's phenomenon not only in persons with congenital or acquired ptosis but also in those with normally functioning lids. Further, a combined opening of the mouth and lid has been observed in normal persons, especially in children, as, for example, when staring or frightened, or, again, when the mouth is involuntarily opened in intense astonishment. Conversely, tight closure of the lid sometimes causes a more or less marked closure of the mouth, especially in children. One must, therefore, assume that the pathologic correlation between lid and jaw is based on a preformed common innervation which exists under normal conditions.

2. Goldstein, K.: Der Aufbau des Organismus, The Hague, Martinus Nÿhoff, 1934.

JUVENILE FAMILIAL AMAUROTIC IDIOCY (VOGT-SPIELMEYER DISEASE)

Review of Literature and Clinical Report of a Case

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OLGA A. G. LITTLE, M.D., NEWTOWN, CONN.

The juvenile type of familial amaurotic idiocy (Vogt-Spielmeyer disease) is a rare disorder, there having been only a few cases reported up to the present time. Particularly few case reports have been published in the United States. In the majority of these the diagnosis was made on the basis of pathologic observations, and this aspect of the disease was especially emphasized.

In view of the fact that the literature has not been reviewed in English and clinical observations are rare, the present study was undertaken. In the case now reported for the first time the clinical, psychologic and electroencephalographic aspects have been emphasized.

HISTORICAL REVIEW OF THE LITERATURE

Since the concept of juvenile familial amaurotic idiocy was originally based on what is known of the infantile form of the disorder (Tay-Sachs disease), it seems best to start this review with a discussion of the latter disorder.

Observations on the eyegrounds of Jewish children, first made by the English ophthalmologist Warren Tay in 1881, were studied from a neurologic point of view. Further detailed clinical observations were made by the American neurologist Sachs six years later, in 1887. The disorder, which since that time has been known as familial amaurotic idiocy, or Tay-Sachs disease, was easily differentiated from other familial diseases of the central nervous system and did not seem to be related to any of the other well known forms of cerebral degeneration. In all the cases published subsequently the clinical symptoms, course and pathologic changes were similar.

Infantile familial amaurotic idiocy is characterized clinically by sudden appearance, after previously normal development, toward the end of the first year of life. It occurs chiefly in the children of Polish and Russian Jews. The cardinal symptoms are blindness, rapidly increasing dementia and paralysis of all extremities, usually of spastic type. The most characteristic signs are the changes in the eyegrounds, namely, optic atrophy and the so-called cherry red spot on the macula lutea. The parents of children with this disorder observe that the patients become increasingly apathetic and that there is regression of intelligence. Later the extremities become paralyzed and in some cases convulsions occur. Physical development becomes arrested, general marasmus is noted and the children die after a rapid downhill course, at the end of the second or third year of life.

From the Emma Pendleton Bradley Home, East Providence, R. I.

The pathologic picture in this disease, which was first studied in 1897 by Kingdon and Russell and later by Schaffer, consists of typical and characteristic changes. The cerebrum usually shows no gross abnormalities. The cerebellum is firm and small in most cases. Histologically, there are generalized alterations in the ganglion cells throughout the central nervous system. The cell bodies are swollen because of deposits of large and small lipoid droplets in the cytoplasm. The dendrites, especially in the region of the cell bodies, have "balloon-like" swellings, approximating in size the cell body. The process in the retina which produces the cherry red spot is identical with that in the brain.

Up to the present no etiologic factor in Tay-Sachs disease is known other than morbid heredity, it being assumed that the disease is the expression of a defect in the germ plasm. Schaffer called it "a disease of the ectoderm," in contrast to Niemann-Pick disease, which, he said, is a process involving lipoid degeneration of the reticuloendothelial system.

In 1903, Batten described, under the title "Cerebral Degeneration with Symmetrical Changes in the Macula in Two Members of a Family," a disorder characterized by progressive mental retardation, loss of vision and loss of motor functions. This disorder differed from the typical Tay-Sachs disease in four respects: (1) It was not limited to Jewish children; (2) the blindness was not accompanied by the same characteristic changes in the eyegrounds; (3) the first clinical symptoms appeared later in childhood, and (4) the course of the disease was slower than that of the original Tay-Sachs disease. In 1906, Vogt published similar observations and, in a detailed clinical discussion, tried to delimit a so-called juvenile form of familial amaurotic idiocy from the original Tay-Sachs disease. His discussion can be summarized briefly as follows: Children who have been in the best of health previously begin to show abnormalities during the school years, usually between the ages of 6 and 14. The onset is gradual and the first symptom is usually progressive loss of vision, which within a few months leads to total blindness. The ophthalmoscopic picture reveals atrophy of the optic nerve head. Mental development becomes arrested, and there is gradual regression to dementia. The motor functions also regress and end in complete paralysis, which in the majority of cases is of spastic type. Death occurs in from five to ten years.

In his publication, Vogt considered only the clinical aspects of the disease. In 1906 and 1907, Spielmeyer first described the pathologic changes in this disorder. His patients were 3 members of one family; the clinical picture in these cases corresponded with that described by Vogt as the juvenile type of familial amaurotic idiocy. The only exceptions in the clinical findings were the presence in all 3 cases of retinitis pigmentosa, in addition to optic atrophy, and epileptic seizures in the later stages of the disease. Spielmeyer described pathologic changes similar to those of the original Tay-Sachs disease.

The findings of Vogt and of Spielmeyer represent the basis for the recognition of the juvenile type of familial amaurotic idiocy.

The first detailed critical review of the literature was published by Schob in 1924. He found that the onset of the disease takes place at the time of the second dentition, i. e., about the sixth year, development having been normal up to this time. There is gradual progressive impairment of vision, ending in total blindness. Parallel with the loss

of vision there is progressive regression of intelligence, terminating in dementia. Epileptic seizures of grand mal type may occur in the early stages of the disease, but are usually observed later. The changes in the eyegrounds in the majority of cases are those of typical retinitis pigmentosa. In a few instances chorioretinitis combined with optic atrophy is noted. The mental changes of juvenile amaurotic idiocy are fairly characteristic. After normal development the child becomes disinterested and apathetic, cannot progress further in school and presents gradual psychic regression. There are restlessness, irritability and sudden laughing or weeping for no reason. Attention, memory and judgment are impaired, and the child gradually forgets what has been learned. Hallucinations and delusions are seldom observed in this disease, but occasionally occur. Speech regresses gradually and disappears entirely in the last stages. Another significant symptom, which Schob stressed, is the disorder of gait. He found in all cases a certain degree of ataxia and unsteadiness, characterized by short groping steps. The terminal stage is marked by spastic diplegia or tetraplegia, the child becoming helpless and requiring constant care. Death usually occurs between the ages of 14 and 16, from intercurrent infection or during status epilepticus. In contrast to the usual occurrence of the original Tay-Sachs disease in Jewish children, the majority of the patients with the juvenile type of familial amaurotic idiocy belong to the Aryan race; both types of the disease have the common tendency to familial incidence.

In spite of his detailed and clear classification of this disease, Schob stressed the fact that the clinical diagnosis of the juvenile type is difficult, and sometimes only presumptive when the cases occur sporadically. The same statement was made by Spielmeyer in 1923, by Higier in 1926 and by others at a later date. All authors agree that this disorder is rarely encountered.

In his monograph published in 1931, Sjögren pointed out that the juvenile type of familial amaurotic idiocy is not as rare as had been assumed in previous publications. He found that the disease occurred relatively often among the Swedish rural population. He described 59 cases of juvenile amaurotic familial idiocy and was able to show that the clinical picture and course were highly uniform. He spoke of a "photographic similarity" in all cases. This usually allows a correct clinical diagnosis, even when the disease occurs sporadically, i. e., when only one member of a family is afflicted. He divided the course of the disease into five stages. Before discussing these, it may be said that Sjögren stressed the importance of the uniform findings in the eyegrounds, as well as the characteristic abnormalities of posture and gait, symptoms which were not emphasized in previous papers.

According to Sjögren, the first stage of the disease is marked by visual disturbance in the form of blindness. The ophthalmoscopic picture is one of retinitis pigmentosa and optic atrophy. The onset usually occurs between the ages of 5 and 8 years and the impairment of vision gradually progresses to total blindness after a course of one or two years. Sjögren found that the average age for development of total blindness was 6.7 years.

The second stage is characterized by the onset of convulsions, which recur in the form of typical grand mal attacks, with unconsciousness and generalized seizures. Sjögren found that the average age for onset of

the convulsions was 11 years. Definite mental changes in the form of lack of emotional control, irritability, restlessness, apathy, and even imbecility, make their appearance at about this time. Speech also shows alterations, such as stammering, explosive articulation and a tendency to repetition of words and syllables.

In the third stage of the disease definite mental deterioration becomes obvious. Attention, memory and judgment are impaired, and the child quickly forgets what he has learned. The personality changes are more severe. The child is entirely disinterested in the environment and is apathetic and irritable. The face is rigid and devoid of expression, but spasmodic laughing and weeping occur. Speech is monotonous and shows marked pressure, and articulation is indistinct. The content of the speech is stereotyped and shows a strong tendency to perseveration. Poverty of words and ideas becomes striking. The child is able to answer only simple questions. In this stage significant neurologic symptoms appear for the first time. All movements become very slow. Typical rigidity and anomalies of posture are present. A characteristic disturbance of this stage is the peculiar gait, the marche à petits pas, a dragging gait with short, slow steps. The knees are flexed and the patient does not lift his feet, but walks with the whole sole on the floor. The arms are not swung in walking, A parkinsonian syndrome may begin at this time. In some cases tremors both of rest and of intention are present. The tendon as well as the superficial reflexes are usually normal. Babinski and Romberg signs may be elicited. Examination of the cranial nerves often reveals nystagmus and strabismus. Sjögren stressed the fact that hearing was intact in almost all cases. Vegetative disturbances in the form of acrocyanosis of both hands and feet were sometimes present.

In the fourth stage the dementia has reached the degree of idiocy. The child is apathetic, fails to take notice of his surroundings and never speaks. The face is expressionless. Speech is limited to a few indistinct and inarticulate sounds. Prolonged screaming and crying are common. The apathy may be interrupted by stereotyped restlessness. The gait regresses rapidly, and the patient eventually walks only with support. The musculature now begins to waste, but still shows good strength. Neurologic and vegetative disturbances become more marked.

In the final, or fifth, stage of the disease the patient is totally demented and paralytic. The child lies helpless in bed, sphincter control is lost and speech is reduced to a few inarticulate sounds. The musculature is now grossly atrophied and partial reaction of degeneration is present. Tendon reflexes are increased and the Babinski sign is positive. Acrocyanosis is marked. Epileptic seizures occur frequently. The patient usually dies in status epilepticus or from intercurrent infection. Sjögren found the average age at death to be about 18 and the course of the disease from ten to fifteen years.

In his investigations on the etiologic and hereditary factors, Sjögren found that the disease is familial and dependent on a recessive, monohybrid hereditary factor. Males and females are affected in about the same frequency.

The pathologic involvement in the juvenile type seems to be essentially the same as that in the infantile form. In their detailed discussion, Greenfield and Holmes (1925) suggested that from a pathologic point

of view two types may be distinguished. In the first the cerebellum is primarily involved. In the second the cerebellum and the rest of the nervous system are affected to an equal degree. Although the pathologic changes are limited to the central nervous system, no part of which ultimately escapes, it appears that this disease has a special affinity for the retina and cerebellum. The retinal lesions, according to Greenfield and Holmes, are of the same nature as those observed in the original Tay-Sachs disease. However, the rods and cones are involved in addition to the ganglion cells, whereas in Tay-Sachs disease only the ganglion cells are affected.

To illustrate the clinical findings in juvenile amaurotic familial idiocy, the following case is reported.

REPORT OF CASE

David, a boy aged 11½ years, was admitted to the Emma Pendleton Bradley Home from an institution for the blind on March 15, 1938, with the chief complaint of progressive changes in personality and unmanageability, of five years' duration.

Family History.—The maternal line was of English and Scotch stock and the paternal line of English stock. The parents were not related. No strain of Jewish blood was present. There was no history of epilepsy, mental or nervous disease, alcoholism, glandular disturbances, polydactylism or syndactylism or other congenital defects. The paternal side of the family showed a strong tendency toward the pyknic habitus. The father was in good health and of pleasant and outgoing personality. He did not use drugs or alcohol. The mother was also in good health but was inclined to worry excessively, particularly about the patient. She admitted having definite swings in mood and stated that she was "nervous," but attributed this to worry over the patient.

The patient had 1 sister, three years his junior, who was attending a small private school because of persistent social and scholastic difficulties in public school. At a summer camp, which she attended in 1938, she failed to follow directions as promptly as the other girls. Because of her extreme sensitivity, tendency to cry at the slightest provocation and anxiety, the camp authorities advised the parents to take her home. Physical examination of this girl revealed nothing abnormal except for a somewhat stiff gait. Mentally, however, she was rather immature in conversation, and there was occasional stammering. At times speech seemed definitely scanning, and it was noted that she tended to repeat certain words, usually at the end of a sentence. At times she repeated the same idea two or three times. She talked about a recent trip in the manner of a child of 4 or 5. Enunciation was clear. When writing her name and the date of her birth, she misspelled her last name and the word "October." It was noted that she was a little too vivacious, overtalkative and giggly. Psychometric tests revealed extremely poor vision and definite retardation in school achievement tests. Tests for general ability and mental control were poorly performed.

Past History.—The patient, David, had been born to a primipara aged 24 after a normal pregnancy. Labor was of twenty-two hours' duration, and delivery was by high forceps. The weight at birth was 8 pounds 7 ounces (3,657 Gm.).

David's infancy was not remarkable. Dentition began at the age of 4 months; he sat up without support at 8 months, talked well at 18 months and walked at 21 months of age. He was considered a bright child, knew the colors at the age of 2 years and could tell time accurately at 4. Nutrition, sleep and excretory

habits were normal. He sustained a laceration of the frontal area of the head at the age of 2 years. The only illnesses were pertussis, at 3; German measles, at 6; measles, at 7; chickenpox and serum sickness, at 11 years of age, and several minor infections of the upper respiratory tract. Previous to the present illness the child had always been happy, pleasant, affable, alert, active and obedient.

Present Illness.—In 1932, at the age of 5½ years, the patient complained of inability to see what was in a nearby truck, which was at close range and was loaded with bricks. Because of this, he was examined by two competent ophthalmologists, whose examinations gave essentially normal results at that time. The boy soon started in school, but did very poorly and seemed to have much difficulty in reading. It was thought by the psychologist that he was a "mirror reader," and a disturbance of lateral dominance was suggested. An ophthalmologist did not agree with this suggestion and prescribed glasses.

In June 1933, at the age of 6½ years, David was seen by another ophthalmologist because of increasing visual impairment. The examination revealed that the boy had optic atrophy and retinitis pigmentosa; the prognosis was guarded because of the possibility of progression. The visual defect increased. Examination in September 1936 revealed left internal strabismus, bilateral nystagmus, pale optic disks and degenerative chorioretinitis. The visual fields were markedly contracted and approached the tubular form.

Because of increasing difficulty in school the boy was transferred to a school for the blind in September 1934. Here his adjustment was poor and he presented a gradual change in behavior. He became excitable, noisy, irritable and negativistic. His schoolwork was very poor, revealing inability to concentrate. He could not grasp Braille and was unable to remember what he had learned in the past. From time to time he attacked children without provocation. He utilized what information he picked up in what seemed to be a bizarre fantasy life. At this time a marked speech defect, consisting of running words together and mumbling, was noted. Speech was under increased pressure. This defect did not respond to treatment, but progressed.

The patient's condition remained unchanged until late in November 1937, at which time he was tearful and talked to himself a great deal. In December 1937 he became acutely disturbed; he was apprehensive, tense, agitated, fearful and hyperactive, and speech was under tremendous pressure. He expressed many somatic delusions, hypochondriacal ideas and feelings of guilt and persecution. He seemed to have unpleasant hallucinations and interpreted every sound as that of an animal or snake that was going to injure him. He was treated for three weeks in a hospital for mental disease, where he became quieter; after a convalescence of one month at home, he returned to the school for the blind. A diagnosis of congenital organic disease of the brain, with optic atrophy, and psychosis with organic disease of the brain was made. For a short period he seemed quiet, but became progressively more active, loquacious, defiant, negativistic, destructive and noisy; for these reasons, he was transferred to the Bradley Home.

Physical Examination.—This revealed moderate obesity and a tendency to the pyknic habitus. The head was somewhat enlarged and asymmetric, due to bulging of the right frontal and left occipital areas. The striking physical finding was blindness. Examination of the eyegrounds showed diffuse pigmentation of both retinal fields, white optic nerve heads and only a few fine vessels. The pupils were unequal, and bilateral internal strabismus was present. There was constant horizontal and upward nystagmus, with the quick component to the right. Other abnormal neurologic findings were a bilateral Babinski and a positive Romberg

sign. There were no tremors other than a slight one of the tongue. The tendon reflexes were normal, but the abdominal and cremasteric reflexes were absent. Posture was poor, with lordosis, round shoulders, bilateral genu valgum, which was more pronounced on the left, and moderate bilateral pes planus. The patient walked with short groping steps, knees flexed and the trunk bent forward.

Mental Examination.—The patient was distractible and unusually aware of and concerned with every noise about him. Speech was under increased pressure, slurring and frequently incoherent. Parts of speech were used incorrectly, and flight of ideas was pronounced. He frequently burst into tears momentarily for no apparent reason. He spoke in great detail of his "broken arm," when in reality all he had was a wart on the dorsum of his left hand. He expressed the idea that he had a "temperature" and "pneumonia." Memory was definitely impaired. He could not relate past incidents without becoming hopelessly confused. Simple tests of retention and recall were poorly performed. He could not recognize voices or sounds that he heard frequently. He repeatedly asked the same questions. Orientation was correct for time but not for place or person. Insight was impaired. He recognized that he was blind, but felt that his eyesight would improve and at times was insistent that he had seen a person or object. Insight into his mental condition was entirely lacking. Judgment was impaired.

Laboratory Data.—Routine laboratory findings were not unusual except that the spinal fluid showed an increase in total protein to 50 mg. per hundred cubic centimeters and the presence of 5 lymphocytes per cubic millimeter, which were larger than average. No other cells were seen. The results of repeated blood counts and urinalyses were within normal limits. The serologic reactions of the blood were negative. The dextrose tolerance curve was within normal limits. The fasting sugar and cholesterol contents of the blood and the basal metabolic rate were essentially normal.

Psychometric Examination.—The Hayes-Binet test for the blind revealed the following findings:

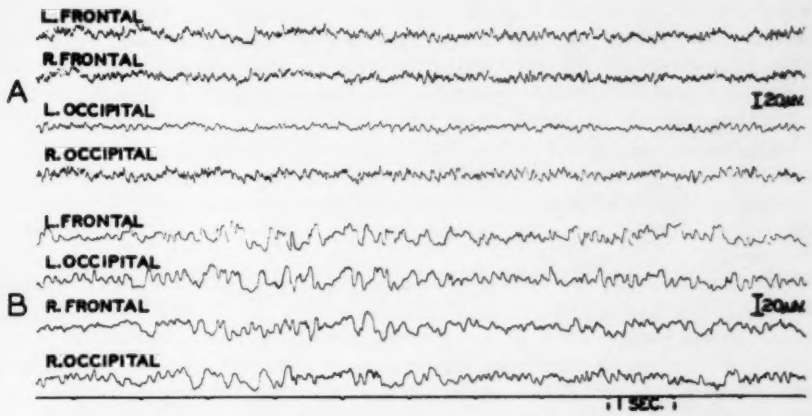
Date	Chronologic Age, Years	Mental Age, Years	Intelligence Quotient
Sept. 28, 1934 *	7-11	7- 0	88
Dec. 19, 1935 *	9- 2	7- 8	84
Jan. 28, 1937 *	10- 3	8- 2	80
March 22, 1938	11- 4	8- 0	71
Sept. 29, 1938 to Oct. 6, 1938	11-11	7- 1	59
April 26, 1939	12- 5	4-10	39

* Test made at the institution for the blind.

The psychologist's comment on the examination in January 1937 is worthy of note: "According to the classification based on clinical tests, the patient's intelligence has deteriorated from about a low average level to almost borderline mental deficiency. Although ordinarily I should not attach much importance to a variation of 8 points in the intelligence quotient, I did consider it significant in this case because four fifths of the blind children entering this kindergarten show a gain of from 5 to 10 points in the intelligence quotient during their first two years in school. The child was most markedly deficient in memory."

Qualitative changes which took place over a period of two years can be followed clearly by comparing this note with the psychologist's comment on the latest examination (April 26, 1939): "Language was almost incomprehensible. As he talked, in a quiet tone, his lips barely moved and his words were spoken so rapidly that many of them could not be understood. He repeated words and phrases in sentences as many as fifteen times, his voice rising with each repetition. Stereo-

typed responses were outstanding; e. g., he seemed to get the set of the phrase and continue to use it as his response to many subsequent questions, such as 'Out the window,' 'Open the window,' 'king and queen.' Such responses were wholly irrelevant to the situation. Comprehension and orientation were very poor. His performance at this time was much less efficient, both quantitatively and qualitatively, than that on Oct. 6, 1938. The two test performances were comparable in several respects; i. e., the wide scatter was evident, with the highest score on vocabulary. [In vocabulary tests he scored at the 10 year level, while he had previously passed this test at the 12 year level.] His first failure had previously been at the 5 year level (on three commissions), but in the present test he failed in naming familiar objects at the 3 year level and in repetition of digits and sentences at the 4 year level. The failure in memory tests at this early level is suggestive in itself of further deterioration. . . . At present he is lower in all types of response, with outstanding deterioration in memory, orientation in time and space and counting."



Electroencephalograms obtained from the patient on March 31, 1939 (record *A*) and May 5, 1939 (record *B*). The latter shows a much more disorganized pattern than the former, and greater abnormality in the form of large slow waves, some of which are of the epileptiform type.

Electroencephalographic Findings.—During the boy's stay at the Bradley Home two encephalographic studies were carried out. Samples of the records appear in the accompanying figure. The first tracings (record *A*), taken on March 31, 1938, showed some abnormality, mainly in the form of 6 per second waves in the frontal and central regions. The records from the occipital regions revealed fairly well defined alpha rhythms and no marked abnormalities. The second electroencephalogram (record *B*), obtained on May 5, 1939, showed much greater abnormality in all regions of the head than did the first. The patterns of activity were badly disorganized, and there were frequent groups of large slow waves, ranging in frequency from 2 to 6 per second. These were sometimes characterized by spike and slow wave patterns and appeared to be indicative of epileptiform activity. In the later records the abnormalities were generalized in all regions of the head, and there was no evidence of localization of the disorder. These records suggested that the abnormalities might originate in the deeper-lying structures of the brain.

Course in Hospital.—Throughout his stay at the Emma Pendleton Bradley Home the patient showed progressive hyperactivity, increased pressure of speech and marked restlessness. During the first part of his stay he exhibited a type of behavior which strikingly resembled a manic psychosis. This was characterized by elated though unstable moods, irritability, flight of ideas, somatic delusions, auditory hallucinations, increased psychomotor activity and lack of insight. His hyperactivity was present both night and day and was not affected by sedatives.

On Aug. 2, 1938 (at the age of 11 years and 9 months) he had the first grand mal convulsion. After this he was exceedingly active, resistive, negativistic, demanding of attention and emotionally labile; he complained of many somatic aches and pains, and his speech became more incoherent. Subsequently he had a number of other convulsions, most of them of grand mal type, which occurred with increasing frequency until his discharge on May 10, 1939. He was discharged from the hospital because of his age and was transferred to a small private school for custodial care. The mental condition of the patient on discharge was as follows: His personality had shown progressive deterioration. The content of his speech and the impulsiveness of his actions were comparable to those of a feeble-minded child. There was lack of emotional control. For no apparent reason he often began to laugh or weep suddenly. Except for these emotional outbursts, his facial expression was blank and empty. Attention, memory and judgment became more disturbed, and he forgot all he had learned.

Treatment.—Because of his restlessness and hyperactivity, a number of sedatives, including pentobarbital sodium, phenobarbital, chloral hydrate and sodium bromide, often in large doses and in various combinations, were given to him during his stay in the hospital. The hyperactivity was usually not controlled by these measures.

In view of the fact that several authors had reported good response to endocrine therapy in cases of the Laurence-Biedl-Moon syndrome, we tried this treatment on our patient over a period of five months. Although doses (approximately equal to the largest which have been reported in the literature) of thyroid, whole pituitary and anterior pituitary were given, there was no apparent effect on the patient, either physically or mentally.

COMMENT

Diagnosis.—All the clinical findings in this case favor a diagnosis of juvenile familial amaurotic idiocy (Vogt-Spielmeyer disease).

Ophthalmologic Findings.—The first symptom was the visual diminution, sudden in onset at the age of 5½ years, after a previously normal development. Although ophthalmoscopic examination gave essentially normal results at this time, one year later an ophthalmologist found that the boy had optic atrophy and retinitis pigmentosa. It may be of interest to quote his report on the first examination.

> The eyes were normal externally. There was good motility in all directions and no nystagmus. Ophthalmoscopic examination showed that the lens and vitreous body of both eyes were clear. The disks were well outlined but rather pale. There were small physiologic excavations. The retinal vessels were slightly smaller than usual. There was disturbance in the retinal pigment. Fine deposits of pigment were distributed throughout the retina of both eyes, especially in the macular area. In the lower half of the fundus on both sides there was little pigment, so that I could see the choroidal circulation.

These ophthalmoscopic findings correspond with those reported by Sjögren (1931), Spielmeyer (1907), Schob (1912), Globus (1923), Nardin and Cunningham (1923), Greenfield and Holmes (1925) and others. All these authors expressed the opinion that in the early stages of the disease it is possible to obtain normal ophthalmoscopic findings in spite of impairment of vision. With the increasing loss of vision, changes in the eyegrounds described by the authors just mentioned were characterized by pale optic disks, small retinal vessels and pigmentary changes in the retina, especially in the region of the macula.

The onset of the disease at the age of 5½ years, with the development of visual difficulty and the subsequent development of optic atrophy and retinitis pigmentosa, corresponds with Sjögren's description of the disease and may be considered the first stage, according to his concept. With the subsequent progress of the disease the ophthalmic findings became more striking. This is clearly shown in the report of the ophthalmologist on a second examination in September 1936, three years after the first.

> There was progressive diminution in vision. When I last saw the patient, in September 1936, the left eye turned in, there was nystagmus of both eyes, the optic disks were pale, the retinal vessels were very small and there was degenerative chorioretinitis in both eyes. I noticed great constriction of the visual fields, as compared with those at the time of the first examination, in 1933. During the first examination I was able to map out a rather definite defect in the upper half of each field, suggesting altitudinal hemianopia. In 1936 the fields were almost tubular.

The ophthalmologic consultant to the Bradley Home reported the results of his examination in April 1938.

> The left eye converged about 30 degrees; perception of light was better in the left eye than in the right, and projection was poor in the right eye and good in the left. The left eye could be turned beyond the midline to the left when stimulated by light, but the excursion was limited. There was coarse, irregular nystagmus, with the quick component in the direction of gaze, which was greatest on looking to the left. The picture was that of retinitis and optic atrophy. With the history of progression, the absence of evidence of inflammatory or vascular change other than narrowing of the vessels, and the presence of typical deposits of pigment (though few), the diagnosis is retinitis pigmentosa.

These rapidly progressing ophthalmic abnormalities are similar to those described by all authors, including Oatman, who in 1911 reported cases of a condition which he called maculocerebral degeneration.

Mental Changes.—Later the patient showed a gradual change in behavior characterized by irritability, restlessness and negativism. His schoolwork became very poor, and there was disturbance of memory. A marked speech defect, with explosive articulation, was noted at this time. These symptoms may represent Sjögren's second stage of the disease, which is characterized mainly by mental changes and the appearance of a marked speech defect. The mental changes were not considered important until recently. Spielmeyer, in his review of the disease in 1923, wrote: "The gradually progressing dementia has no specific characteristics which enable one to recognize the disease." Later papers, especially those of Sjögren, Marinesco, Norman, and FitzJerrell and

Neuchiller, stressed the importance of the gradual changes in behavior in patients with this disease. These changes are restlessness, irritability, lack of emotional control and impairment of attention, memory and judgment. The children gradually forget what they have learned. Our patient illustrated this well. All psychometric tests indicated gradual but marked regression of mental function. The speech defects in our case, in the nature of increased pressure, stereotypy and perseveration, corresponded to those in the cases of Sjögren and others. As the disease progressed further, the child suddenly became acutely disturbed by fearful ideas, flight of ideas, definite hallucinations and delusions. According to Sjögren, acute psychoses with hallucinations and delusions sometimes occur, but are rare. The first case reported by FitzJerrell and Neuchiller is comparable to ours in this respect. He reported that his patient had delusions of persecution and paranoid ideas, and that the subsequent behavior strikingly resembled that in manic psychosis. True manic psychosis, however, is rarely found in children, according to Kasanin.

Physical Configuration.—The obesity, which the patient presented on admission, may appear to be somewhat unusual for this disease. However, Ritter, in 1932, described 2 cases of a condition definitely diagnosed as Vogt-Spielmeyer disease in which the obesity was the most striking symptom for a long period.

Convulsions.—With the onset of the first grand mal attack, at the age of 11¾ years, the second stage of the disease may be considered as having been concluded. The occurrence of epileptic seizures, of grand mal form, in the early stages of the disease is mentioned in almost all the cases reported. The seizures usually appear long before other neurologic symptoms can be observed.

Further Progress.—With advance of the disease, one finds in this case all the typical symptoms represented in Sjögren's third stage of the disease. First, regressive intellectual changes continued until the level of feeblemindedness was reached. Speech defects increased and vocabulary became poorer. We were able to follow these changes by psychometric examinations, which, together with the examiner's comments, proved the gradually progressive mental deterioration.

In addition to the clinical symptoms and the results of psychometric examinations, this progressive cerebral deterioration was clearly demonstrated in the electroencephalographic records. The first record revealed some abnormalities, but the second, taken a little more than one year later, showed much more marked disorganization. This disorganization was present in almost all regions, with no particular localization. The occurrence of epileptiform waves, together with bursts of slow waves, of 2 to 6 per second frequency, and the irregularity of the alpha waves seem to be the characteristics of the picture. This second record appears in some respects to be similar to one published in another connection by Kornmüller and Janzen, which was taken from a patient with suspected amaurotic idiocy (the diagnosis was confirmed later by histologic examination of the brain).

During the course of the illness several neurologic symptoms also developed, of which, according to Sjögren, the disturbance of gait was most outstanding and characteristic. This disturbance of gait was also described as an obvious symptom by Vogt (1906), Schob (1912),

Frenkel and Dide (1913), Globus (1923), Russetzki (1927) and others. Schob stated that this disturbance is similar to that in senile astasia-abasia. Our patient walked with short groping steps, the knees flexed and the arms held without swinging—a gait which may be characteristic of blind persons. However, Sjögren stressed that this so-called marche à petits pas is typical of this disease and can be found in almost all cases.

In this stage of the disease, Sjögren and others described the development of parkinsonian symptoms. Those observed in our patient were the typical rigidity, with slowing of all movements, the aforementioned marche à petits pas, the blank and rigid facial expression, nystagmus, tremor of the tongue, abnormality of posture and a positive Romberg sign.

The tendon reflexes were normal but the superficial reflexes were absent in our case. Schob (1912), Nikula (1922) and Westphal and Sioli (1925) described hyperactive abdominal reflexes in their cases; the other authors found normal superficial reflexes. Our patient had a positive Babinski sign, which, according to Sjögren, occurs inconstantly in the minority of cases, and then only in the last stages of the disease. In the cases described by Vogt, Berger and Nikula there was a positive Babinski sign.

The increased frequency of the epileptic seizures in this advanced stage appears to be in accordance with that observed in most of the cases reported.

Sjögren is the only author who has reported the results of examination of the spinal fluid. In the majority of cases there were no pathologic changes, but he stressed the fact that a slight positive Pandy reaction occurred. We did not perform a Pandy test, but the increase in total protein may be regarded as confirmatory.

In summary, it may be said that the clinical picture in our case fits well with that of Vogt-Spielmeyer disease. The course of the disorder can be traced through all the stages described by Sjögren as characteristic of the juvenile type of familial amaurotic idiocy. At present the condition of the patient represents the end of the third stage of this disease. It will be of value and interest to follow the further course and to prove the clinical diagnosis by histologic examination.

Differential Diagnosis.—In view of the conformity of the picture in our case with Sjögren's description of this disease, the differential diagnosis does not appear to be difficult. The following conditions, however, should be considered.

Laurence-Biedl-Moon Syndrome: This disease is characterized by five cardinal symptoms, namely: dystrophia adiposogenitalis, retinitis pigmentosa, mental retardation, polydactylism or syndactylism and familial occurrence. Although in many cases reported the clinical picture did not fulfil all these requirements, the Fröhlich syndrome together with some other deformity, such as polydactylism or syndactylism, congenital nystagmus or strabismus, congenital cataract, atresia ani or even retinitis pigmentosa (which Biedl himself called a congenital deformity), was present in almost all cases. Furthermore, clinically the Laurence-Biedl-Moon syndrome is not a progressive disorder, and the pathologic picture is not known. Biedl suggested that it represents a syndrome of deformities in which obesity forms only one of the most striking items.

Laurence and Moon, in the title of their monograph, spoke of "retinitis pigmentosa accompanied by general imperfection of development." Although our patient appeared to be somewhat obese, his condition did not seem to fulfil all the requirements of the Fröhlich syndrome. The genitalia, though small, were not typical. Furthermore, there are several reported cases of Vogt-Spielmeyer disease in which obesity was one of the most striking symptoms. There were no indications of polydactylism or syndactylism or other congenital deformities in our patient, his sibling or his ancestors. The average age of patients with the Laurence-Biedl-Moon syndrome is more variable and, in the majority of cases, is higher than that in Vogt-Spielmeyer disease. The obesity and mental retardation, outstanding symptoms of the Laurence-Biedl-Moon syndrome, are manifest in early childhood, long before other symptoms can be observed. On the other hand, the patients with Vogt-Spielmeyer disease develop normally in every respect up to the time of the second dentition. The psychic disorders in the Laurence-Biedl-Moon syndrome, as Ritter pointed out, are essentially those of feeblemindedness, whereas the psychic disorders in Vogt-Spielmeyer disease are similar rather to those of an organic dementia. The repeated convulsive outbreaks, which were present in our case and which occur in more than 80 per cent of all cases of Vogt-Spielmeyer disease, have never been reported in cases of the Laurence-Biedl-Moon syndrome.

The age of onset, development and course of our patient's illness and the marked speech defect, personality changes, disturbances of gait, convulsions and neurologic findings are characteristic of the Vogt-Spielmeyer disease, and thereby exclude the Laurence-Biedl-Moon syndrome.

Juvenile Dementia Paralytica: When accompanied by optic atrophy, this disease may sometimes produce a clinical picture which is similar in certain respects to that of juvenile familial amaurotic idiocy. In addition to the positive serologic reactions and other syphilitic stigmas, such as Hutchinson teeth, osteitis or periosteitis, saddle nose, interstitial keratitis and disturbances of hearing, the disease can be differentiated by the course and development of the amaurosis. In Vogt-Spielmeyer disease one sees bilateral chorioretinitis with impairment of vision, which ends finally in total blindness. Chorioretinitis is seldom seen in juvenile dementia paralytica and usually does not produce such pronounced diminution of vision. The neurologic symptoms, which in Vogt-Spielmeyer disease are essentially extrapyramidal, are typically pyramidal in juvenile dementia paralytica.

Cerebral Sclerosis: The cerebral sclerosis of Scholz is characterized by a rapid course, absence of the degenerative retinal changes and deafness.

Other Disorders: There are other rare diseases which may sometimes produce a clinical picture similar to that of Vogt-Spielmeyer disease. Among these are the cerebral sclerosis of Krabbe, the cerebral sclerosis of Pelizaeus and Merzbacher, Friedreich's ataxia, Marie's hereditary cerebellar ataxia with spasticity and acquired hydrocephalus of various origins. All these can be easily differentiated from the Vogt-Spielmeyer disease when one considers the latter's typical onset, course and development, with the characteristic stages and symptoms, and when one remembers that in all cases of Vogt-Spielmeyer disease there is such conformity that, with Sjögren, one can speak of a "photographic similarity" in the great majority of cases.

SUMMARY

A review of the literature on the juvenile type of familial amaurotic idiocy (Vogt-Spielmeyer disease) is presented, and a case is reported.

Behavior resembling a manic psychosis was an unusual feature in this case.

Repeated psychometric and electroencephalographic examinations presented graphic evidence of the progressive nature of the patient's disorder, which is reported essentially from a clinical point of view.

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CEREBRAL CHANGES IN ROCKY MOUNTAIN SPOTTED FEVER

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In Rocky Mountain spotted fever, cerebral disturbances are as common as they are in the classic spotted (typhus) fever, namely, headache, restlessness, hyperesthesia, lethargy, delirium, occasional convulsions and muscular rigidity.[1a] The histologic neural changes in the brains of patients dying of typhus fever have been extensively studied, especially abroad, and are classified as meningoencephalitis. In reports of cases of Rocky Mountain spotted fever in man the changes in the central nervous system are only casually referred to, but they have been studied a great deal in animals. Because of the clinical similarity between these two morbid entities, which may be so great that one is occasionally mistaken clinically for the other,[1b] the pathologic features of the two diseases also would be expected to be similar. A histopathologic study of the brain of a victim of Rocky Mountain spotted fever, which was placed at my disposal by Dr. M. G. Bohrod of Peoria, Ill., proved this to be a fact.

REPORT OF A CASE

History.—A white girl aged 11 was admitted in a comatose condition to the Methodist Hospital of Central Illinois, Peoria, where she died a half-hour later.

Eleven days previously the patient had been bitten by a tick on a farm. She complained of headache and vomited. Six days after she was bitten her hands and feet were covered with a rash and she became comatose. A brother of the patient, who also became sick after a tick bite, recovered.

Examination.—Dr. G. M. Kelby and Dr. S. M. Miller reported the following findings: Confluent purpuric rash over the body, hands and feet; somewhat enlarged pupils, which reacted sluggishly to light; a dry tongue and sordes on the lips; absence of tendon reflexes; marked rigidity of the neck, and a definite Kernig sign. The spleen extended 2 fingerbreadths below the costal margin.

The spinal fluid contained 10 cells (type not specified) per cubic millimeter; the total protein and sugar contents were 45 and 72 mg., respectively, per hundred cubic centimeters; no micro-organisms were demonstrated.

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1. (*a*) Wolbach, S. B.: Studies on Rocky Mountain Spotted Fever, J. M. Research **41**:1 (Nov.) 1919. (*b*) Lumsden, L. L., and Tucker, C. B.: Clinical and Epidemiological Features and Differential Diagnosis of Rocky Mountain Spotted Fever and Endemic (Murine) Typhus Fever, J. Tennessee M. A. **32**:339 (Oct.) 1939. (*c*) Anderson, J. F.: Spotted Fever (Tick Fever) of the Rocky Mountains: A New Disease, Bulletin 14, United States Treasury Department, Public Health Service, 1903.

Necropsy.—This was performed by Dr. M. G. Bohrod. His report follows: "The brain was wet and heavy, and weighed 1,630 Gm.; the small blood vessels about the cortex were markedly distended, giving the surface a light pink hue; the meninges were slightly cloudy; the kidneys, spleen and liver exhibited cloudy swelling, and petechial hemorrhages were present in the skin."

Microscopic Observations.—The subarachnoid space was distended and contained large lymphocytes with pyknotic nuclei, mesothelial cells, fibroblasts, polyblasts (which were in some areas more, in others less, numerous), plasma cells and broken-up red cells. An unusual feature was the presence of histiocytes, which were packed with lipoids and formed distinct foci (fig. 1). No noteworthy changes, such as thrombi or perivascular infiltrations, were present in the meningeal blood

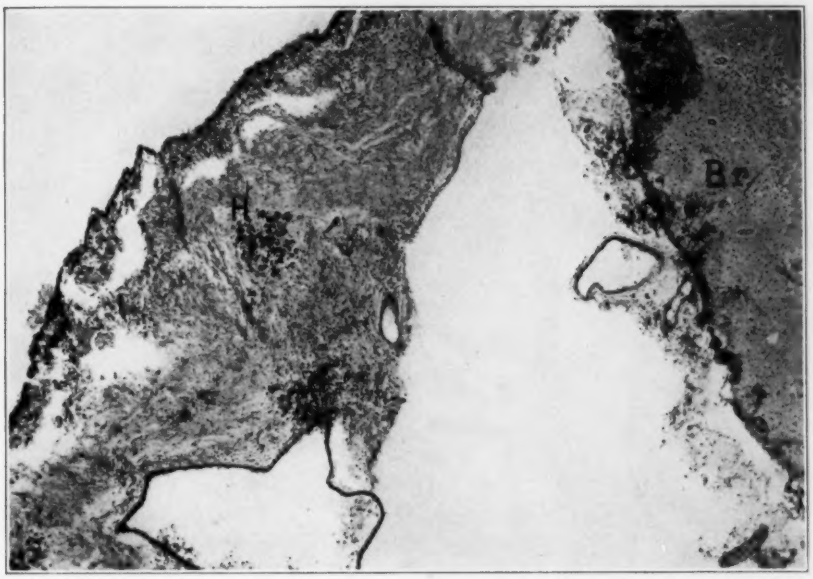

Fig. 1.—A focus of histiocytes (*H*) packed with lipoids in the subarachnoid space. *Br* indicates the brain.

vessels. The histologic picture was that of aseptic meningitis, which was in evidence over the cerebral convexity and the base of the brain, including that of the cerebellum.

The ganglion cells throughout the brain exhibited slight tumefaction of their bodies and processes and chromatolysis, without signs of neuronophagia or satellitosis. In the olivary bodies the ganglion cells were, in addition, homogeneous; their nuclei were irregular and poor in chromatin, but the cell bodies were rich in fatlike substances. Such substances were observed in other regions of the brain and were gathered in the perikaryon in the form of drops and droplets. Granules of lipoids were present also in the oligodendrocytes, the ependymal cells of the ventricles, the tuft cells of the choroid plexus and the adventitial walls of the blood vessels and capillaries (fig. 2). Around the blood vessels the lipoids were in the form of large globules mixed with minute ones, and stained densely green with

toluidine blue. In some areas—the optic thalamus and the occipital lobe—the infiltrations with lipoids were sometimes so intense that they marked the course of the branches of the blood vessels. The capillaries, however, were infiltrated only slightly. Aside from the presence of lipoids in the adventitial spaces, the blood vessels exhibited practically no changes. In some blood vessels the lipoid accumulations were mixed with lymphocytes and occasionally with plasma cells, but distinct cellular infiltrations with the formation of cuffs were not seen. In smaller blood vessels and capillaries the adventitial cells were somewhat hyperplastic and the endothelial cells were slightly tumefied, but not sufficienty to affect the size of the vascular lumens.

Glia: No noteworthy changes were observed in the glia. Astrocytes were rare; the oligodendrocytes were occasionally swollen, and some exhibited karyor-

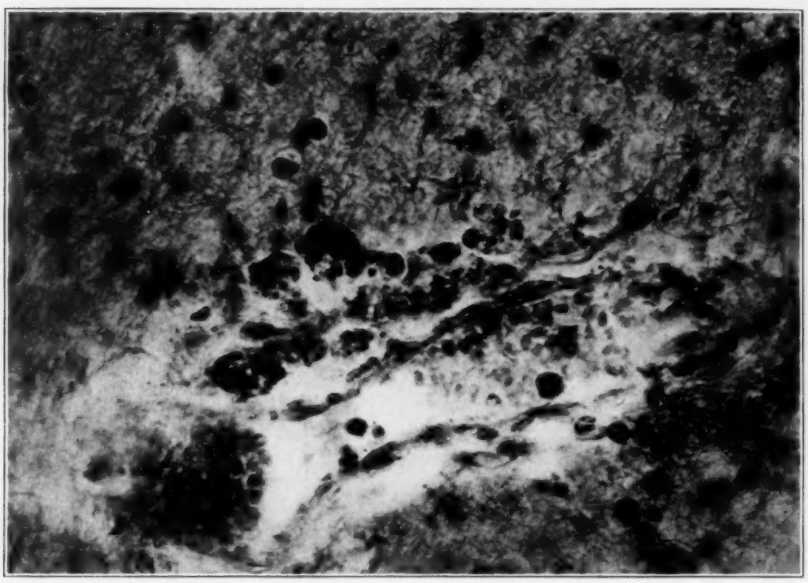

Fig. 2.—Histiocytes packed with lipoids around a small blood vessel. Holzer stain.

rhexis with hyperchromatosis. On the other hand, microgliocytes were conspicuous, especially in the molecular layer of the cerebellum, without the bushlike formations described by Spielmeyer in encephalitis accompanying typhus fever. The microgliocytes were numerous in the vicinity of nodes or nodules—dense aggregations of nuclei. Such aggregations (fig. 3) were scattered throughout the brain, including the brain stem and the spinal cord (only the upper portion was available for study), and were occasionally represented by fragments. For this reason their size varied, and in some regions, the cerebellum for instance, they were large enough to traverse the entire width of the molecular layer. The elements which made up a nodule were practically always naked nuclei, only a few of which possessed a small amount of cytoplasm. The nuclei were multiform, round, oval or oblong, often irregular and usually poor in chromatin. No ganglion cells were present in the nodules, which as a rule were avascular. Only rarely could a capillary be discerned buried in the mass of the nuclei, which much resembled

similar nuclei in the nodes observed in typhus fever encephalitis.[2] Their mesodermal nature could be excluded; that is, they were not fibroblasts or microgliocytes, but probably oligodendrocytes or glia nuclei. No micro-organisms could be demonstrated in them, but Dr. Bohrod succeeded in locating organisms in the adventitial spaces.

SUMMARY AND COMMENT

The histologic features were mild inflammatory and degenerative changes and were combined with aseptic meningitis. The changes may be summed up as those of nonsuppurative meningoencephalitis, and on the whole were analogous to those of typhus fever encephalitis. The presence of nodules was characteristic of the encephalitis associated with both typhus and Rocky Mountain spotted fever, although nodules

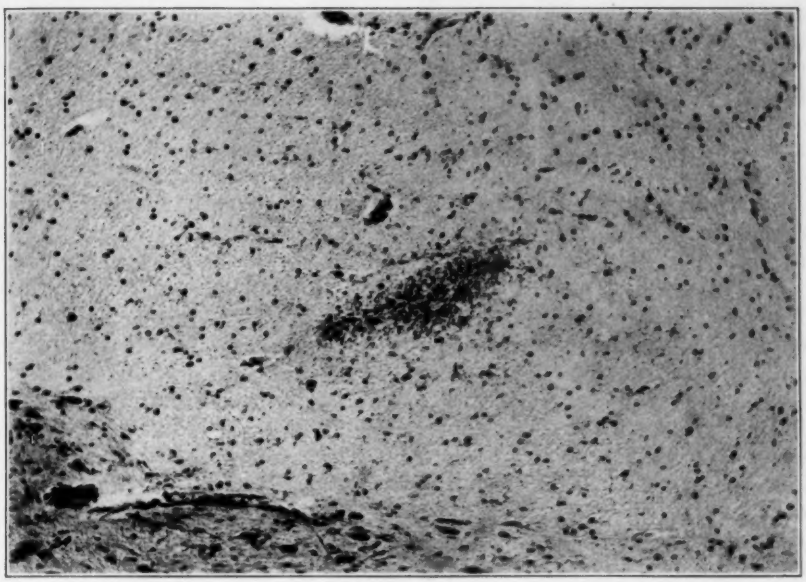

Fig. 3.—A nodule in the medulla oblongata. Toluidine blue stain.

may be present also in other types of meningoencephalitis—lethargic, poliomyelitic or toxoplasmic encephalitis, Borna disease or the form caused by trichiniasis or malignant endocarditis—or any other severe infection of the central nervous system. In encephalitis due to infection with Trichina and Toxoplasma the nodules and the perivascular infiltrations contain parasites; in the form occurring is Rocky Mountain spotted fever the parasites are present in the perivascular or adventitial infiltrations, but not in the nodules. The focal cell accumulations, with formation of adventitial infiltrations and nodules, are probably a manifestation of a local tissue reaction to the presence of an invader

2. Hassin, G. B.: Brain Changes in Typhus Fever Contrasted with Those in Epidemic Encephalitis and Acute Poliomyelitis, Arch. Neurol. & Psychiat. **11**:121 (Feb.) 1924.

—a topic which has been discussed elsewhere.[3] It was thought that the number, and especially the localization, of the nodules was specific of some forms of encephalitis. For instance, in typhus fever encephalitis the nodules are prevalent in the medulla, and such a localization has been asserted by some authors to be characteristic of the disease. However, this is not always the case. In the present case nodules were as promiscuous in the medulla as elsewhere in the central nervous system.

Another feature deserves attention, namely, the accumulation of lipoids in the ganglion cells, adventitial and subarachnoid spaces and some glia cells. While one may encounter lipoids in the brain under normal conditions, their excessive amounts in children should be considered pathologic—a manifestation of a degenerative condition caused by a noxious agent. Their presence in the subarachnoid space in this case was unquestionably secondary to their invasion from the adventitial spaces of the cerebral blood vessels. A glance at figures 1 and 3 may convince one that the histiocytes (*H*) around the blood vessels and those in the subarachnoid space and their contents are similar. However, accumulation of lipoids occurs also in typhus fever encephalitis or in any other infection of the central nervous system, such as lethargic encephalitis, in which lipoids were described by Bassoe and me.[4]

The changes described are thus not typical of any particular form of encephalitis. Only the demonstration of a specific infectious agent is of decided diagnostic value. So far, such an organism has not been found in common types of encephalitis as the lethargic or poliomyelitic form or that associated with typhus fever, but is demonstrable in encephalitis accompanying Rocky Mountain spotted fever, trichiniasis and toxoplasmic infection. The differences in the various types of encephalitis are thus etiologic, regardless of the fact that the pathologic features are identical. The etiologic factor in Rocky Mountain spotted fever is Rickettsia, which is undoubtedly responsible for the inflammatory changes and, through the toxins elaborated by them, for the degenerative changes. Such an explanation is probably valid also for the cerebral histologic changes occurring in the typhus and lethargic types of encephalitis, thus rendering invalid the view that the changes in the brain described here are vascular.

Another difference, at least between the encephalitis of Rocky Mountain spotted fever and that produced by typhus fever, is serologic. Lumsden and Tucker [1b] emphasized that in cases of the latter agglutination with Bacillus proteins X 19 is practically always present in high dilutions, but is absent in many cases of Rocky Mountain spotted fever, and that the latter disease is transmitted by infected ticks and the former by fleas.

Knowledge of the clinical history and the proper evaluation of pathologic data, in short, a combination of clinical, pathologic and serologic facts, is of decisive value in establishing a correct diagnosis.

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3. Hassin, G. B., and Diamond, I. B.: Trichinosis Encephalitis: Pathologic Study, Arch. Neurol. & Psychiat. **15**:34 (Jan.) 1926.

4. Bassoe, P., and Hassin, G. B.: A Contribution to the Histopathology of Epidemic ("Lethargic") Encephalitis, Arch. Neurol. & Psychiat. **2**:24 (July) 1919.

In conclusion, I wish to state that the cerebral changes produced in animals [5] infected with Rocky Mountain spotted fever are practically the same as those observed in man.

CONCLUSIONS

1. The histologic changes of the central nervous system in Rocky Mountain spotted fever are those of nonsuppurative meningoencephalitis.

2. The encephalitis is histologically analogous to the type produced by typhus fever and other forms of severe encephalitis.

3. Although on the basis of histologic studies of the central nervous system a diagnosis of this disease is not decisive, one may assume with certainty that in Rocky Mountain spotted fever the central nervous system is fundamentally involved.

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5. Lillie, R. D.; Dyer, R. E., and Topping, N. H.: Cerebral Pathology in Rodents in Endemic Typhus and Rocky Mountain Spotted Fevers, Pub. Health Rep. **54**:2137 (Dec. 1) 1939.

ABERRANT LOCATION OF SUBDURAL HEMATOMA

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The location of subdural hemorrhage over the cerebral hemisphere is so uniform that trephination of the squamous portions of both temporal bones of the skull or of both frontal and occipital bones generally is considered sufficient exploration to rule out the presence of such a hematoma if nothing of significance is seen. We have found this exploratory method inadequate in several instances.

The boundaries of the usual subdural hemorrhage may be described somewhat as follows: The clot covers the cerebral cortex from the tip of the frontal lobe to the tip of the occipital lobe. It is limited mesially by the superior longitudinal sinus; inferiorly, it rarely extends for any distance over the temporal lobe, the inferior border of the hemorrhage corresponding roughly to a line parallel with the sylvian fissure. Exceptions to this localization have been noted, but they are extremely rare. Dandy [1] has seen a subdural hemorrhage over the lateral surface of the temporal lobe, and another in the sella turcica. Peet [2] had a case of subdural hemorrhage in the latter location and another in which the hemorrhage covered the posterior surface of both cerebellar hemispheres in an infant. Munro [3] has recorded a case of subdural hematoma that was located over both cerebellar hemispheres.

Three cases of subdural hematoma of unusual location are here recorded. Postmortem examination was performed in all.

REPORT OF CASES

CASE 1.—E. H., a Negro aged 45, who was admitted to the neurologic service of the Cincinnati General Hospital on May 1, 1938, had been found unconscious on the floor of his room that morning. His employer, at whose home he resided, said that he had appeared to be normal on the previous morning. He had had occasional bouts of epistaxis for about three years. Sometimes this bleeding lasted as long as twelve to twenty-four hours. The history was otherwise uninformative, except that he had drunk alcoholic liquors to excess once or twice a week for many years. On May 2, a friend of the patient appeared at the hospital and stated that on the morning of April 30 he had seen the patient fall backward,

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From the Laboratory of Neuropathology, Cincinnati General Hospital, and the Departments of Internal Medicine (Neurology) and Surgery, University of Cincinnati College of Medicine.

1. Dandy, W. E.: The Brain: Subdural Hematoma, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., vol. 12, pp. 295-306.

2. Peet, M. M.: Extradural Hematoma, Subdural Hematoma, Subdural Hydroma, in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1940, chap. 7, pp. 133-159.

3. Munro, D.: The Diagnosis and Treatment of Subdural Hematomata, New England J. Med. **210**:1145-1160, 1934.

striking his head with violence on a cement pavement. This blow rendered him unconscious for several minutes. He then arose and fell again. When assisted to his feet he was unable to stand, and was carried to his room and put to bed.

Examination.—The abnormal findings on admission to the hospital were: coma, from which he could not be aroused; occasional yawning; abrasions over the left malar region and left tibia; some dried blood in the nares, and a blood pressure of 162 systolic and 102 diastolic. Divergent squint was noted; the corneal reflexes were not obtained, and the patient had left hemiparesis, which included the left lower portion of the face. The extremities were normally resistant to passive movements. The tendon reflexes were more active on the right than on the left, and the plantar responses were of extensor type bilaterally.

Roentgen examination of the skull revealed no fracture. A lumbar puncture was performed on admission to the ward. The initial pressure was 120 mm. of water; the cerebrospinal fluid was bloody, and after centrifugation the supernatant fluid was slightly xanthochromic. The fluid contained 75 mg. of protein per hundred cubic centimeters, and the colloidal gold curve was 0012321000. The Wassermann reactions of the blood and cerebrospinal fluid were negative.

Course.—The patient recovered consciousness on May 2. His temperature, which was normal on admission, arose to 101.5 F. on May 2 and fluctuated between 98.6 and 102 F. until his death. The pulse rate fluctuated between 80 and 134, but was usually around 110. Twelve hours before death the pulse rate dropped rather abruptly from 115 to 60. The rate of respiration was 14 on admission; it rose to 25 shortly thereafter and gradually increased during his stay in the hospital to a high of 50 per minute, twelve hours before death.

On May 2, the patient roused from coma, and ptosis of the right eyelid was observed; at this time the right eyeball was deviated toward the right. The left hemiparesis was confirmed. The cerebrospinal fluid pressure on this day was 80 mm. of water; only enough fluid was removed to determine that it was bloody (12,000 red cells per cubic millimeter). After centrifugation, the supernatant fluid was xanthochromic. The cerebrospinal fluid pressure on May 3 was 100 mm. of water. The xanthochromic fluid contained 2,060 red blood cells per cubic millimeter. The colloidal gold curve was normal. On this day constant twitching of the left foot and leg was first noted (epilepsia partialis continua). These convulsions continued unabated until the operation on May 7; they did not spread to the upper extremity. The clonic movements ceased when he sank into stupor and returned when he was awakened. On May 6 the patient was stuporous and uncommunicative. The optic disks were normal. Ocular movements were possible in all directions. The left pupil was 5 and the right 4 mm. in diameter; they reacted promptly, but through a small range, to flashlight. The neck resisted flexion. Paralysis of the left extremities had become complete. The lower portion of the left side of the face was weak. Resistance of all extremities to passive movement was normal. The patient apparently appreciated painful stimuli on both sides of the face and in all extremities. The tendon reflexes were equal in the two upper extremities; in the lower, the right knee jerk was the only reflex obtained and was hypoactive. The plantar responses were extensor on both sides, being more marked on the left than on the right. Hyperpiesis was maintained throughout the course in the hospital (the systolic pressure being between 145 and 240 and the diastolic between 95 and 140 mm. of mercury).

Operation.—On May 7 four exploratory trephine openings were made in the skull. These were placed in both lateral posterofrontal and in both lateral parieto-occipital regions. On opening the dura over the right frontal lobe, a thin subdural

blood clot was observed and evacuated. Nothing abnormal was seen in the other areas. The intracranial pressure was not increased.

Postoperative Course.—The condition of the patient was not altered by the operation. On May 9 ptosis of the right eyelid was again obvious when the patient was aroused. The right eyeball was deviated far to the right, and rested in the outer canthus. On May 10 the patient lapsed into coma, from which he could not be aroused. His pupils were equal and reacted well to flashlight. There developed signs of bronchopneumonia, with rising temperature and pulse and respiratory rates, and he died on May 13.

Before the operative procedure it was obvious, because of the continuous jacksonian seizures of the left lower extremity, that the lesion was situated

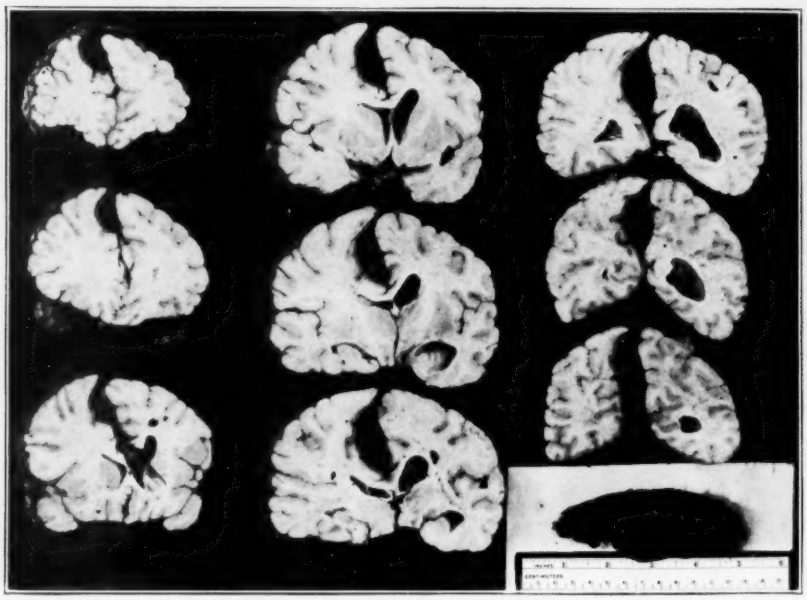

Fig. 1 (case 1).—Photograph illustrating the location of a subdural hemorrhage between the cerebral hemispheres. Vertical sections are 1 cm. in thickness. Note the ventricular compression and shifting.

superiorly in the right frontal lobe in or near the motor strip. The lesion was thought to be in the nature of trauma of the brain, probably a subdural hemorrhage. On the day after admission to the hospital the patient appeared too well to have had a massive cerebral hemorrhage extending into the subarachnoid space or ventricle.

Autopsy.—This was performed fifteen hours after death. The right pupil measured 4 and the left 5 mm. in diameter; the right eye was fixed in marked lateral deviation.

Postmortem examination was limited to the cranium. The four trephine openings were noted, and it was observed that the substance of the brain had protruded a distance of 1 cm. through each of them. The brain and the dura covering the

vertex were removed intact. Exploration of the cranial cavity revealed no fracture. There was a marked cerebellar pressure cone. The convolutions of the cerebral cortex were flattened and the sulci obliterated. After the brain had been fixed in dilute solution of formaldehyde U. S. P. (1:10) for ten days it was sectioned. On reflection of the dura from over the right convexity of the cerebrum, a large subdural clot was found; it occupied the space between the hemispheres. The hematoma was bounded superiorly by the dura, mesially by the falx and laterally by the mesial surface of the right hemisphere (frontal, parietal and occipital cortex). At autopsy the clot appeared dark red and of jelly-like consistency, and measured 11 cm. in anteroposterior extent and 4 cm. superoinferiorly at the point of its greatest depth. The cerebral hemispheres were sectioned vertically in blocks measuring 1 cm. in thickness (fig. 1). These blocks revealed marked compression of the right cerebral hemisphere. The right lateral ventricle, the right half of the corpus callosum, the superior half of the right lateral ventricle and the right basal ganglia were compressed and dislocated downward.

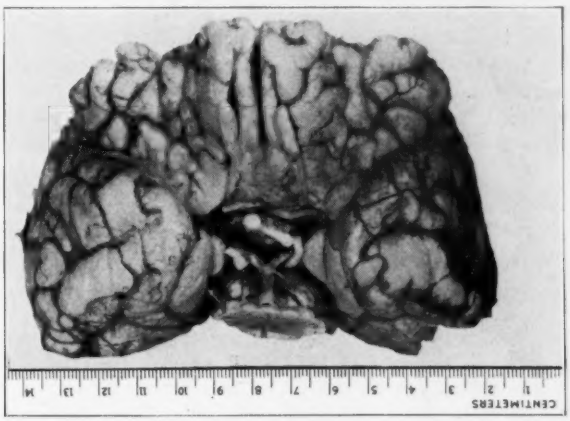

Fig. 2 (case 2).—Photograph of the base of the brain showing the tentorial pressure cone of the uncus. Note the blood-stained arachnoid covering the left temporal lobe.

Summary.—A man aged 45 sustained a severe blow to the occiput. Bilateral frontal and occipital exploratory trephination, which is usually considered sufficient from a diagnostic standpoint, revealed a thin subdural hematoma in the right frontal region. At autopsy a large subdural hematoma was observed lying between the falx and the mesial surface of the right cerebral hemisphere.

CASE 2.—D. T., a Negress, aged 68, was admitted to the medical service of the Cincinnati General Hospital on Feb. 13, 1940, in deep coma. A diagnosis of diabetes mellitus had been made at this hospital in 1938, and her history taken at that time indicated that the disease had been present at least since 1936. The patient died forty hours after admission. Clinical study had indicated that she had diabetic coma with acidosis, lobar and lobular pneumonia (type III Pneumococcus), hypertensive and arteriosclerotic heart disease and generalized vascular sclerosis. There was no history of trauma, and she did not sustain any trauma to the head during her stay in the hospital. The patient roused somewhat twenty-

four hours after admission. She was noisy and confused, so that restraint was necessary. There was no finding in the history or examinations that led one to suspect a subdural hemorrhage. The Wassermann and Kahn reactions of the blood were positive. Spinal puncture was not done. Close relatives, interviewed after the postmortem examination, could not add to the history that had been previously elicited from them; they knew of no instance of trauma.

Autopsy.—This was performed three hours after death. Abnormalities other than those in the central nervous system were: lobar and lobular pneumonia, syphilitic aortitis, aortic atherosclerosis, and fatty infiltration of the liver. After removal of the calvarium, a reddish blue, fluctuant mass was seen and palpated beneath the dura in the left temporal region. When the dura was incised a large blood clot escaped from the subdural space of this region. No fracture of the skull was seen. The brain weighed 1,100 Gm. It was fixed in dilute solution of formaldehyde U. S. P. (1:10) for seven days and then sectioned. The arachnoid overlying the left temporal lobe was blood stained. This staining was limited superiorly by the sylvian fissure. It extended over all the temporal convolutions, and was maximal over the second and third convolutions. Inferiorly, it stopped rather sharply at the lateral border of the uncus. Anteriorly, it extended to the temporal pole; posteriorly, it extended over the occipital lobe to a point 3 cm. from the occipital pole. The other points of note in the brain were: bilateral uncal herniation, that on the right measuring 6 and that on the left 4 mm. in width (fig. 2); mild cerebellar pressure cone, and numerous soft yellow plaques in the vessels of the circle of Willis.

Summary.—A woman aged 68, without any history suggestive of trauma, entered the hospital in coma. At autopsy a rather fresh, large subdural hematoma was observed covering the lateral and inferior surfaces of the left temporal and occipital lobes.

Case 3.—M. V., a white man aged 70, who was admitted to the neurosurgical service of the Cincinnati General Hospital on Oct. 6, 1938, had fallen forward on his face on a sidewalk on October 5. Shortly thereafter he was confused and nauseated, and vomited. On the following morning he lapsed into coma, from which he could not be aroused. He was then admitted to the hospital, where he lived for forty-eight hours.

Examination.—On admission to the hospital the temperature was 102 F., the pulse rate 100 and the respiratory rate 24. The blood pressure was 190 systolic and 110 diastolic. The heart was enlarged. A large ecchymotic area was located above the left eye. There were extravasation of blood into the left conjunctiva and dried blood in the left nostril. There were numerous abrasions about the body, particularly of the right thumb and first finger. Crepitation and false motion were elicited in the distal portion of the terminal phalanx of the first finger of the right hand. The patient was in deep coma, from which he could not be aroused. The pupils were 2.5 mm. in diameter; they reacted through a small range to light. The right limbs were flaccid. The tendon reflexes were hyperactive throughout. The plantar responses were of extensor type. Lumbar puncture revealed a cerebrospinal fluid pressure of 125 mm. of water. The fluid was grossly bloody.

Operation.—This was performed two hours after the patient's admission to the ward. Trephination of the left temporal region revealed a very thin subdural clot. The dura was left open for drainage. A right frontal trephine opening revealed nothing abnormal.

Course.—The temperature and pulse and respiratory rates gradually rose. The patient never recovered consciousness. Occasionally the upper extremities moved, particularly the left. On the morning of May 7, the respirations were noted to be of the Cheyne-Stokes variety. A lumbar puncture on this day revealed cerebrospinal fluid pressure of 300 mm. of water. The patient died eighteen hours after termination of the trephine exploration.

Autopsy.—Postmortem examination, made seven hours after death, revealed the following abnormalities other than those in the nervous system: terminal acute

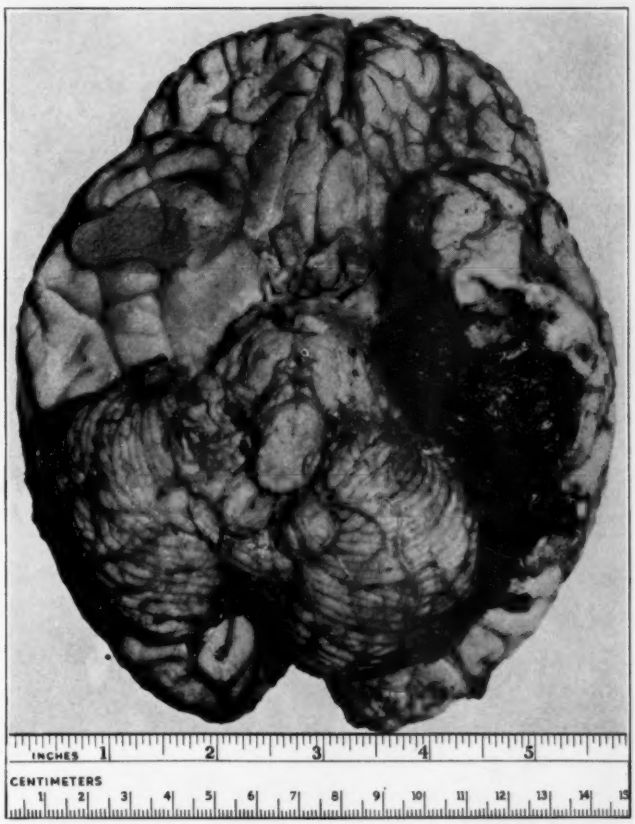

Fig. 3 (case 3).—Photograph of the base of the brain showing subdural hemorrhage beneath the left temporal lobe.

bronchitis and confluent lobular pneumonia; myocardial degeneration and fibrosis, and moderately advanced generalized arteriosclerosis.

The brain weighed 1,500 Gm. It was fixed in dilute solution of formaldehyde U. S. P. (1:10) for twelve days before sectioning. No fracture of the skull was observed. There was a moderate amount of subarachnoid hemorrhage over the right parietal area; otherwise the right cerebral hemisphere appeared to be normal. The left cerebral convexity was normal. Beneath the left temporal lobe there was a large subdural clot (fig. 3), which extended backward, overlying the tentorium,

and laterally to cover a portion of the third temporal convolution. The hematoma measured 8 cm. in an anteroposterior direction, 4.5 cm. in width and 2.5 cm. in its superoinferior plane. A large uncal herniation was present on the left. There was a cerebellar pressure cone. The arteries of the circle of Willis were moderately sclerotic and contained occasional plaques. The brain was sectioned

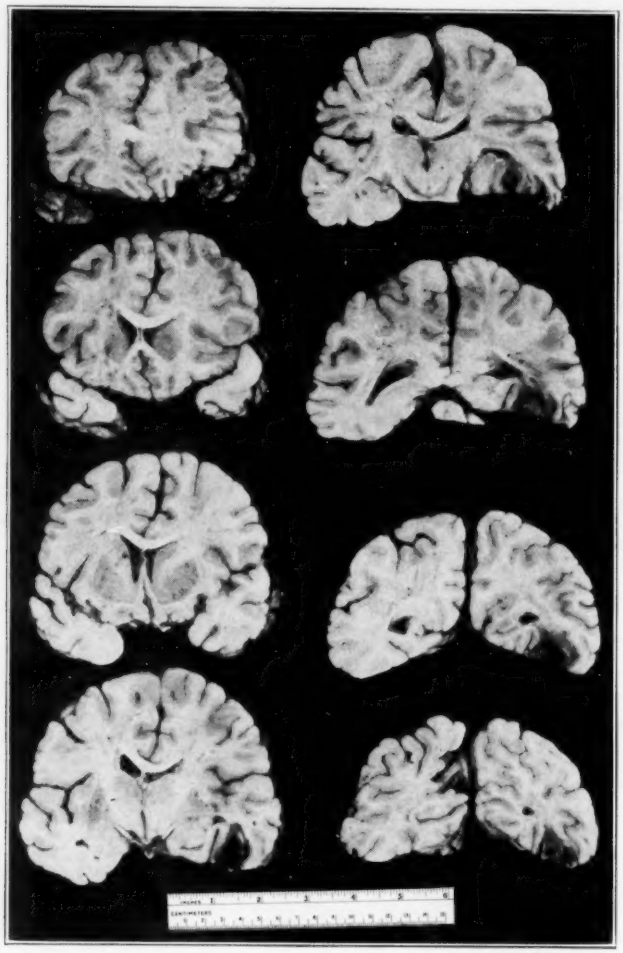

Fig. 4 (case 3).—Photograph of the cerebral hemispheres sectioned vertically, illustrating (1) compression of the left lateral ventricle, (2) shifting of the ventricular system from left to right and (3) infarction of the inferior temporo-occipital region on the left.

vertically into blocks measuring 1 cm. in thickness. The changes in the hemispheres are best illustrated by a photograph (fig. 4). There had occurred some shifting of the ventricular system (lateral and third ventricles), as well as neural tissues, from left to right. This was apparently due chiefly to edema, which

was most readily seen and measured as an increase in the bulk of the white matter. Compression of the left lateral ventricle may be seen in figure 4. Compression of the left temporal lobe had occurred from below and probably was mechanically responsible for some of the shifting and compression of the ventricles and gray structures in the midline. The area supplied by the left posterior cerebral artery was infarcted (fig. 4). The infarction was similar to that described by Jefferson[4] and by Reid and Cone.[5]

Summary.—A man aged 70 sustained a severe trauma to the head and lapsed into coma twenty-four hours later. Bilateral temporal trephination, which is usually considered a sufficient exploratory procedure, revealed a thin subdural hemorrhage over the left lateral temporal area. The patient succumbed eighteen hours later; the diagnosis was intracerebral hemorrhage. Post mortem a large subdural hematoma was observed lying beneath the left temporal lobe. Infarction of the left posterior cerebral artery, which presumably resulted from reduction of blood flow in the artery, secondary to its constriction between the herniation of the uncus and the relatively rigid third nerve (Jefferson; Reid and Cone), was concluded to have occurred as a secondary manifestation of the large subdural hemorrhage and the herniation of the uncus of the left temporal lobe through the cerebellar tentorium.

COMMENT

The occurrence of hemorrhage in any of the subdural spaces above the tentorium may be expected if one keeps in mind the usual location and the anatomic relations of the bridging veins. "Bridging veins" is a term the application of which Hannah[6] limited to the superior cerebral veins which cross the subdural space to the longitudinal sinus. Leary,[7] on the other hand, applied this term to the veins which cross the subdural space, traveling between the arachnoid and the dura, and which do not empty directly into any sinus. Leary[7] noted that standard textbooks of anatomy do not mention these veins, which are so delicate that they are easily broken and overlooked in the removal of the brain. He found that the bridging veins occur most frequently in four locations: (1) Veins which cross from the arachnoid of the convexity of the cerebral hemisphere to the dura at a distance of from 1 to 4 cm. from the superior longitudinal sinus. They are most often observed in the frontal region, but they may be seen over the parietal convexity. (2) Veins traversing the subdural space from the arachnoid of the base of the temporal lobe to the dura covering the middle fossa, and to the tentorium. (3) Veins from the pole of the temporal lobe to the dura covering the sphenoid bone. (4) Subtentorial bridging veins, which Leary concluded are not important from the stand-

4. Jefferson, G.: The Tentorial Pressure Cone, Arch. Neurol. & Psychiat. **40**:857-876 (Nov.) 1938.

5. Reid, W. L., and Cone, W. V.: Mechanism of Fixed Dilatation of the Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030-2034 (May 20) 1939.

6. Hannah, J. A.: Etiology of Subdural Hematoma: Anatomical and Pathological Study, J. Nerv. & Ment. Dis. **84**:169-186, 1936.

7. Leary, T.: Subdural or Intradural Hemorrhages? Arch. Path. **28**:808-820 (Dec.) 1939.

point of subdural hemorrhage. These are groups of veins which are familiar to the neurosurgeon and which limit indiscriminate manipulation with a brain spoon when exploring the subdural space or when evacuating clot from it.

Leary noted that if bridging veins are present in one of these locations they will also be present in the other regions. He described their delicate histologic structure and commented on the slenderness of the barrier between the contained blood and the subdural space.

The diagnosis of these aberrant subdural hematomas is somewhat more difficult than that of subdural hemorrhages which occur in the usual location. There is no "syndrome of subdural hemorrhage," as the manifestations of this disorder are protean. An attempt to set up a clinical picture as typical of this disease only misleads the general practitioner, into whose hands cases of this type most often fall. We consider the factors most helpful in the diagnosis of subdural hemorrhage to be the following, in the order of their importance: (1) Constant vigilance for the condition and suspicion of its presence in every case in which symptoms and signs indicate cerebral disease, particularly those in which either "stroke" ("shock") or "mental disease" has been suspected or in which the patient is in coma. This suspicion should be inversely proportional to the age of the patient, but should not be dismissed in any case until the possibility of the hematoma is thoroughly exhausted. (2) A history of trauma. This is often difficult to obtain, particularly in the general hospital practice of medicine; for this reason, we have found it secondary in importance to the first factor. Every effort should be made to obtain a story of trauma, and the anamnesis should be carried back for many years. In the absence of a history of trauma, bruises, abrasions or scars about the body or blood in the nares, ears or mouth are rather reliable substitutes. (3) Abnormal cerebrospinal fluid. The cerebrospinal fluid pressure is usually, but not always, increased at all stages of the disease. The fluid practically always contains blood in the early days of the disease. If the puncture is made from one to three weeks after the trauma to the head the fluid may be xanthochromic.

There is no other constant factor short of a surgical procedure that will aid in the diagnosis of subdural hemorrhage. It follows that a certain number of unnecessary exploratory trephinations will be performed in search of this condition. In our experience this procedure has never retarded the patient's chances of improvement, and in cases in which a clot is found it may be said to be a life-saving factor. In the last analysis one cannot disagree with Munro,[3] who stated that in his experience the diagnosis of subdural hemorrhage can be made only by exploration.

With respect to the diagnosis in the 3 cases here recorded: In case 2, in which the patient was known to have had diabetes and entered the hospital in coma, subdural hemorrhage was not suspected. It is probably fair to say that subdural hemorrhage would not have been suspected even had the patient been seen by a "neurologically minded" person brought up on the tenets which have previously been listed as the important factors in the diagnosis of subdural hemorrhage. A lumbar puncture might have been helpful. It may be a fair premise that

lumbar puncture should be performed on all patients who are in coma when first seen (Solomon and Aring [8]). It might be well to add to this rule the condition: "if they do not improve after a *short* interval of indicated therapy."

In case 1 the employment of ventriculographic examination was discussed but was not resorted to. In case 3 a limited exploration was made. Too much reliance was placed on a clinical impression that the maximal signs of impairment were in the upper extremity, whereas facial weakness was minimal. The ipsilateral pupil was not dilated. Therefore, a lesion low in the temporal fossa was not considered likely. In this case, also, ventriculographic examination might have been of help, though probably its use would have been attended by greater danger than in case 1.

The ventriculographic procedure under such circumstances has been recommended by Dandy, and has been employed by others. Bull [9] recently reviewed the subject in some detail. He found it almost uniformly possible to confirm the diagnosis of subdural hematoma by the encephalographic or the ventriculographic method. Use of the latter would seem to be the only means of locating aberrant hematomas. Its employment in cases of acute hematoma calls for fine judgment. Should the interpretation of the plates be erroneous there may be revealed at operation either intracerebral hemorrhage or recent softening. If intracerebral hemorrhage is present, probably the best therapy is evacuation. If the softening is massive enough to be mistaken for subdural hemorrhage clinically, the same therapy might hold for this condition, depending on the location of the lesion.

Therefore it is concluded that in cases of suspected subdural hematoma in which exploration (by means of bilateral temporal trephine openings, or by means of bilateral frontal and occipital trephine openings) has given negative results, the ventriculographic procedure should be employed in a further effort to determine the location and the nature of the disease process.

The routine exploratory procedure adopted in the neurosurgical service of the Cincinnati General Hospital in cases of suspected subdural hematoma is as follows: In cases of acute hemorrhage bilateral temporal trephine openings are employed. If indicated by the findings, these openings may be enlarged to the size of a decompression, permitting further exploration of the subdural space. Acute subdural and epidural hemorrhages may easily be confused. This approach permits exposure of the middle meningeal artery and of the foramen spinosum if epidural hemorrhage should be found.

In cases of suspected subacute and chronic hematoma, bilateral frontal and occipital burr holes are placed. If the hematoma is found it can be dealt with as necessary. Should the exploration reveal nothing abnormal, one has already placed the burr holes, which later may be employed for ventriculographic examination.

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8. Solomon, P., and Aring, C. D.: A Routine Diagnostic Procedure for the Patient Who Enters the Hospital in Coma, Am. J. M. Sc. **191**:357-361, 1936.

9. Bull, J. W. D.: The Radiological Diagnosis of Chronic Subdural Hematoma, Proc. Roy. Soc. Med. **33**:203-224, 1940.

SUMMARY

1. Three cases of subdural hemorrhage are recorded, in which the great mass of the clot was located (1) between the cerebral hemispheres, (2) over the lateral temporal area and (3) beneath the temporal and occipital lobes, respectively.

2. In 1 of these cases the hematoma was not located by use of the ordinary trephine exploration through the squamous portions of both temporal bones. In another the hemorrhage was missed by exploration through bilateral frontal and occipital trephine openings.

3. In cases in which the presence of subdural hemorrhage is strongly suspected, ventriculographic examination should be used in addition to trephine exploration when the latter fails to reveal a clot.

TREATMENT OF TRIGEMINAL NEURALGIA WITH VITAMIN B_1 (THIAMINE HYDROCHLORIDE)

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Trigeminal neuralgia has recently been included among the various conditions in which benefit is claimed from large doses of parenterally administered vitamin B_1. However, there has been no discussion of the possible mechanism of action of this substance, and none of the experiments to determine its therapeutic value for this condition appear to have been adequately controlled.

Trigeminal neuralgia is a disease the cause of which is unknown. Its pathogenesis is not clear, and no conclusive pathologic picture has been described. It is a disabling disease of middle and late adult life, characterized by attacks of momentary sharp flashes of pain over the distribution of one or more divisions of the fifth cranial nerve and by a chronic remitting course. As the disease progresses the attacks tend to become more severe and to last longer, and the remissions, which often vary remarkably in duration, tend to become shorter. Since careful examination of the patient usually gives no clue, the cause of the pain may be attributed to many factors. Similarly, spontaneous remissions occurring during the course of some form of therapy may be attributed to the treatment. Until the present time there has been no report of reliable data which will satisfactorily indicate what is to happen in a given case. Experience shows that the course of the disease in one patient is no indication of what it will be in another. The frequency and severity of attacks of pain may be constant in one patient, but irregular and wholly unpredictable in another. It is generally accepted that classic trigeminal neuralgia is relieved by surgical transection of the posterior root of the trigeminal nerve. Yet it is not infrequent to find cases in which the diagnosis is trigeminal neuralgia but the pain is not relieved by posterior root section. Hence the experimental approach to the subject from the standpoint of therapy is hazardous. Evaluation of results is faced with many difficulties.

Borsook, Kremers and Wiggins [1] treated 58 patients with trigeminal neuralgia "with large doses of vitamin B_1, and in some cases in addition with concentrated liver extracts rich in the anti-pernicious anemia principle."[1b] The vitamin B_1 was given intravenously and the

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1. Borsook, H.; Kremers, M. Y., and Wiggins, C. G.: (*a*) The Relief of Symptoms in Major Trigeminal Neuralgia Following the Administration of Massive Doses of Vitamin B_1 Supplemented in Some Instances by Concentrated Liver Extract, Science **89**:439 (May 12) 1939; (*b*) The Relief of Symptoms of Major Trigeminal Neuralgia (Tic Douleureux) Following the Use of Vitamin B_1 and Concentrated Liver Extract, J. A. M. A. **114**:1421 (April 13) 1940.

liver extract intramuscularly. The patients were observed for from six to fourteens months. The results are summarized as follows:

> So far, thirty-seven are markedly improved, fifteen improved, three slightly improved, and three not improved. Of the fifty-two patients markedly improved and improved, thirty-eight had a remission in the course of and after active therapy which was longer than any spontaneous remission during the two years prior to the beginning of treatment.[1b]

Other reports have been limited to the results of treatment in only a few cases. Bakhsh [2] treated 7 patients, of whom 4 obtained relief and 2 about 30 per cent improvement. Aring, Evans and Spies [3] stated that thiamine hydrochloride given intravenously in doses of from 50 to 100 mg. daily over a period of ten days to patients suffering from severe pain (carcinoma, tumor of the cord and brachial and trigeminal neuralgia) did not act as an analgesic.

This study was stimulated by the encouraging reports of Borsook, Kremers and Wiggins and was undertaken in an attempt to evaluate vitamin therapy by a comparison of observations on patients so treated with those on control subjects. Eight patients with clinically typical trigeminal neuralgia were treated in the following manner: Four patients (cases 1, 2, 3 and 4) were given a high vitamin diet, supplemented with brewers' yeast and a concentrate of fish liver oil, and parenteral administration of thiamine hydrochloride. Three were given intramuscular injection of sterile water alone. One patient was given intramuscular injections of sterile water for two weeks followed, without interruption, by intramuscular injections of thiamine hydrochloride.

EXPERIMENTAL SUBJECTS

CASE 1.—O. P., a woman aged 46, complained of recurrent attacks of pain in the right lower part of the face for four years. An injection of alcohol three years ago was followed by relief for two years. Nine months ago another injection of alcohol gave no immediate relief, although the pain gradually subsided after several weeks. When treatment was begun the pain had been present for several weeks and was of moderate severity.

Treatment.—Daily injections of thiamine hydrochloride in doses of from 10 to 20 mg. were given for eleven days. She received a total of 145 mg.

Result.—The pain improved on the fifth day and disappeared on the ninth day of treatment, leaving residual soreness of the face. Ten months after treatment was discontinued the patient reported that she had had an occasional twinge of pain but no real attack.

CASE 2.—A. S., a woman aged 76, had suffered from recurrent attacks of extreme pain in the right lower part of the face of increasing severity and duration for three years. The present attack had lasted six months and had been totally incapacitating for two weeks. An injection of alcohol two days prior to beginning of treatment gave only partial relief.

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2. Bakhsh, I.: Treatment of Nervous Diseases by Vitamin B_1, with Special Reference to Trigeminal Neuralgia: Report of Seven Cases, Indian M. Gaz. **74:** 456 (Aug.) 1939.

3. Aring, C. D.; Evans, J. P., and Spies, T. D.: Some Clinical Neurologic Aspects of Vitamin B_1 Deficiencies, J. A. M. A. **113:**2105 (Dec. 9) 1939.

Treatment.—Daily intramuscular injections of thiamine hydrochloride were given in doses varying from 10 to 50 mg. for ten days. A total of 340 mg. was given.

Result.—The attacks of pain gradually diminished in severity and disappeared on the eighth day of treatment. The patient's daughter wrote nine months after treatment was stopped that the patient had had several short attacks of moderate severity.

CASE 3.—H. S., a man aged 56, complained of severe attacks of pain in the left lower part of the face for seven weeks. For three days he was unable to chew or to move his face without inciting an attack of pain.

Treatment.—Daily intramuscular or intravenous injections of thiamine hydrochloride were given in doses varying from 10 to 100 mg. each for ten days, and then on alternating days during the following eighteen days. He was given a total of 530 mg. in twenty-eight days.

Result.—During the first ten days the pain subsided gradually and disappeared, but during the fourth week of active therapy the pain returned with increased severity, necessitating cessation of this form of treatment. An injection of alcohol gave prompt relief.

CASE 4.—M. T., a woman aged 54, had suffered from sharp flashes of pain in the right cheek and forehead intermittently for six months. For two weeks the pain had been very severe and frequent.

Treatment.—Intramuscular or intravenous injections of 100 mg. of thiamine hydrochloride were given daily for four days, and then on alternate days for ten days. A total of 900 mg. was given in two weeks.

Result.—There was questionable relief after several days of treatment, but the discomfort and incapacity were of such severity that an injection of alcohol was resorted to on the fifteenth day, with immediate relief.

CONTROL SUBJECTS

CASE 5.—R. G., a man aged 62, complained of intermittent pain over the entire right side of the face and forehead for two years. It had been very severe for two weeks. He had had a similar attack of pain twenty-six years before, which had persisted intermittently for about one and one-half years and was unrelieved by injection of alcohol and by dental extraction.

Treatment.—Two cubic centimeters of sterile water was injected intramuscularly daily for six days.

Result.—The pain was much improved on the fourth day and had entirely disappeared on the sixth day of treatment. Six months later the patient reported that he had had no return of pain.

CASE 6.—S. S., a woman aged 59, complained of flashes of pain in the left cheek and upper gum intermittently for approximately eighteen years. The attacks varied in duration and severity. One year ago, an attack lasting six months was unrelieved by an injection of alcohol. The present attack was of two weeks' duration and moderate severity.

Treatment.—Two cubic centimeters of sterile water was injected intramuscularly six days a week for three weeks, then twice a week for three weeks.

Result.—The pain improved gradually during the first ten days and then disappeared, leaving residual sensitiveness of the skin and gums. Two months later the patient reported that she had had an occasional twinge of pain but no real attack.

CASE 7.—A. McG., a woman aged 60, complained of intermittent attacks of pain in the right lower part of the face for six years. The first attack lasted two months; the second attack, five years before, lasted two months, and the third attack, two years before, was relieved several weeks after an intraoral injection of procaine hydrochloride. The present attack began three months before and had not been relieved by an intraoral injection of procaine hydrochloride or by a subsequent intraoral injection of alcohol, at another hospital, two weeks ago.

Treatment.—Four cubic centimeters of sterile water was injected intramuscularly daily for seven days.

Result.—The pain was entirely relieved on the third day of treatment. After three months, during which she had been entirely free from pain, the patient returned to the clinic because of a mild attack of pain. An additional dose of sterile water gave prompt relief.

CASE 8.—M. B., a woman aged 50, had had several attacks of intermittent pain in the right cheek and forehead for two years. The attacks were relatively mild until five months ago. At this time she was admitted to a hospital in Panama, where she was given daily intramuscular "injections of vitamin B" and tablets of brewers' yeast by mouth for one month. The pain gradually disappeared. Three weeks ago the pain returned with greater severity. She was anxious to repeat the "vitamin B treatment."

Treatment.—Fifteen injections of 4 cc. of sterile water, given daily six days a week, were followed without knowledge of the patient, by thirteen intramuscular injections of 100 mg. of thiamine hydrochloride, each dose being dissolved in 4 cc. of water.

Result.—On the ninth day of treatment she considered that the pain was approximately "50 per cent improved" but continued to have attacks of moderate severity. Two days after the injections of thiamine were begun the pain disappeared and she felt better in general. However, on the seventh day after the beginning of the thiamine paroxysmal attacks of pain returned. Because of the patient's discouragement and continued incapacity, an injection of alcohol was given with immediate complete relief of the pain.

COMMENT

Four patients with trigeminal neuralgia were treated by oral administration of vitamin concentrates and parenteral injections of vitamin B_1 (thiamine hydrochloride). Two patients (cases 1 and 2) improved while under treatment and 2 (cases 3 and 4) did not improve. Four other patients were treated by intramuscular injections of sterile water. Three of these patients (cases 5, 6 and 7) improved promptly, but the fourth (case 8) failed to improve satisfactorily, even after the substitution of thiamine hydrochloride for the sterile water. It is our interpretation that the 5 patients who improved (cases 1, 2, 5, 6 and 7) entered on a natural remission of the disease, which was not affected by the treatment given, except for the partial psychologic relief derived

from constant medical care, and that the other 3 (cases 3, 4 and 7) had attacks of such severity and persistence as to require interruption of the nerve by injection of alcohol. Follow-up reports on the 5 patients who improved show no essential difference between the condition of the 2 who received vitamin therapy and that of the 3 who received sterile water. The variation in frequency, duration and severity of the attacks of pain in trigeminal neuralgia, as well as many other factors in the disease, makes the evaluation of any form of therapy which does not have an immediate effect extremely difficult.

CONCLUSION

It is probable that vitamin B_1 (thiamine hydrochloride) has no specific beneficial effect on trigeminal neuralgia.

Technical and Occasional Notes

ELEMENT OF OPTICAL ILLUSION IN APPEARANCE OF PRESERVATION OF AXIS-CYLINDERS IN CERTAIN LESIONS OF THE CENTRAL NERVOUS SYSTEM

LEO ALEXANDER, M.D., BOSTON, AND TRACY J. PUTNAM, M.D., NEW YORK

In studying certain lesions of the central nervous system with myelin sheath stains of the Weigert type and with axis-cylinder stains (Bielschowsky, Bodian) we observed that a striking appearance of discrepancy between involvement of the myelin sheaths and that of the axis-cylinders (preservation of axis-cylinders) with the low power lens may become less striking in inverse proportion to the degree of magnification; if high power objectives are used and actual counts are made the discrepancy may appear either insignificant or nonexistent. By counting the number of persisting myelin sheaths and axis-cylinders in a large series of lesions we have found that in many of the lesions in which low power views suggested complete or relative preservation of axis-cylinders the damage to them was in reality similar or equal to that of the myelin sheaths. Since most illustrations in the literature contrasting the preservation of axis-cylinders and the destruction of myelin sheaths in adjacent sections are given at low magnification, this finding seems to us to be of general interest.

The fact can be well exemplified in lesions of secondary degeneration of several years' standing in which the loss of myelin sheaths and that of axis-cylinders is bound to be equal. Figures 1 *A* and 2 *A* show Weigert-stained sections through the degenerated pyramidal tract at the level of the medulla oblongata and the thoracic region of the cord, respectively, in such a case. The degenerated portions of the pyramidal tract are outstandingly demyelinated. Figures 1 *B* and 2 *B* show sections from neighboring blocks stained for axis-cylinders. The diminution in size of the degenerated right medullary pyramid and of the affected left lateral column of the cord can be recognized, but at low magnification no area of less intensive staining comparable to the pale areas in the myelin sheath stains can be seen. If this lesion were thought to be primary, and was not a known secondary degeneration, the low power views would suggest preservation of axis-cylinders.

High power views, however, show that the degree of involvement of axis-cylinders and that of myelin sheaths in this lesion are identical. This can be seen by comparing *A* and *B* of figure 3, which show part of the normal left anterior pyramidal tract in a Weigert and in a Bodian stain, respectively, with *A* and *B* of figure 4, which show part of the degenerated right anterior pyramidal tract in a Weigert and in a Bodian stain, respectively, at the same high magnification. Actual

From the Department of Neurology, Harvard Medical School, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

counts reveal that the number of axis-cylinders in each field of the degenerated pyramidal tract is identical with that of the myelin sheaths.

The fallacious impression presented by the low power views seems, therefore, to belong in the category of optical illusions, and we decided to analyze its character by a simple experiment with optical patterns.

A and *B* of figure 5 are schematic diagrams representing myelin sheaths and axis-cylinders in their approximate arrangement in normal white matter. In figure 5 *A* the myelin sheaths are drawn in solid black and the axis-cylinders and the interspaces are left white, thus giving a schematic interpretation of the general appear-

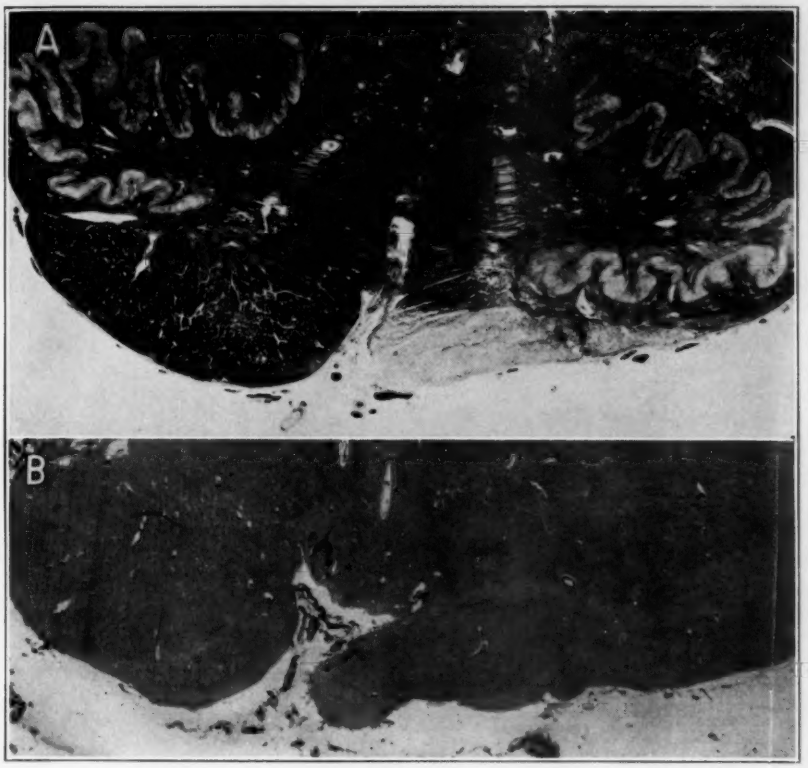


Fig. 1.—Degeneration of the right pyramidal tract of the medulla oblongata following hemorrhagic softening of the right internal capsule, of several years' standing. × about 6.5. *A*, Weigert-Pal stain; *B*, Bodian stain for axis-cylinders.

ance of Weigert-stained preparations. In figure 5 *B* the axis-cylinders are drawn in solid black; another thin black ring around each of them denotes the outer circumference of each myelin sheath, while the lipoid body of the myelin sheath has been left white. The resulting appearance of solid black axis-cylinders within a thin, honeycombed framework consisting of outer lamellae of myelin sheaths is a schematic impression of the general appearance of axis-cylinder stains (compare with figure 3 *B*). The glial reenforcements of this framework [1] and the glial network

1. Alexander, L.: The Neurone as Studied by Microincineration, Brain **61**:52-61, 1938.

itself are not represented. In figure 6 *A*, the myelin sheath schema, and in figure 6 *B*, the axis-cylinder schema, equal numbers of nerve fibers have been deleted in exactly corresponding places. The result is a sharply outlined focus of demyelination in the myelin sheath schema (fig. 6 *A*), while in the axis-cylinder schema (fig. 6 *B*) the lesion appears not sharply outlined, with apparent preservation of a number of axis-cylinders, which seems to exceed the number of myelin sheaths preserved in the other diagram (fig. 6 *A*).

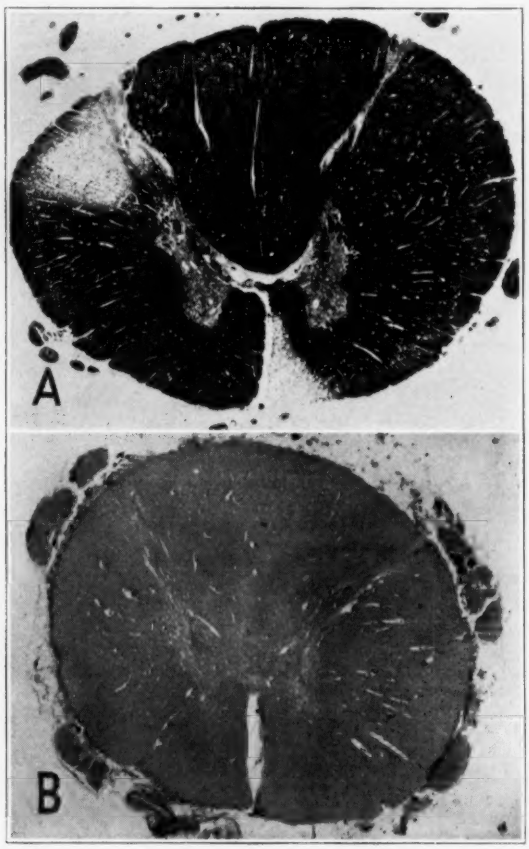


Fig. 2.—Degeneration of the left lateral and right anterior pyramidal tracts of the spinal cord in the same case as that shown in figure 1. × 8. *A*, Weigert-Pal stain; *B*, Bodian stain.

The fact that the adjacent surfaces of myelin sheaths touch each other closely in normal tissue gives the tissue as a whole a solid bluish black appearance. Any disruption of its continuity is bound to appear in exaggerated intensity in a low power view. Axis-cylinders are separated from each other mainly by the intervening layers of myelin sheaths. Although every axis-cylinder is stained solid black, which exceeds in darkness even that of the myelin sheath in a Weigert-stained preparation, the low power impression of silver-stained specimens is that of a

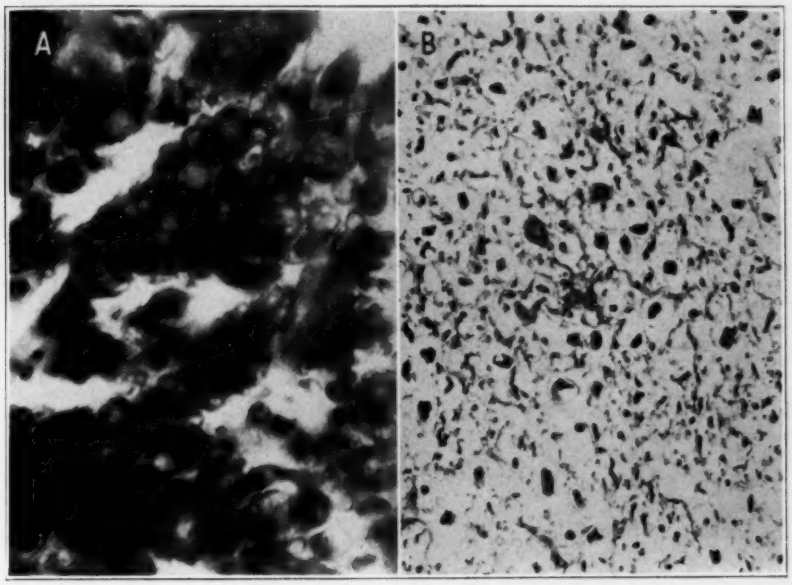


Fig. 3.—High power enlargement of the normal left anterior pyramidal tract of the spinal cord from the same case as that shown in figures 1 and 2. × 530. *A*, Weigert-Pal stain; *B*, Bodian stain.

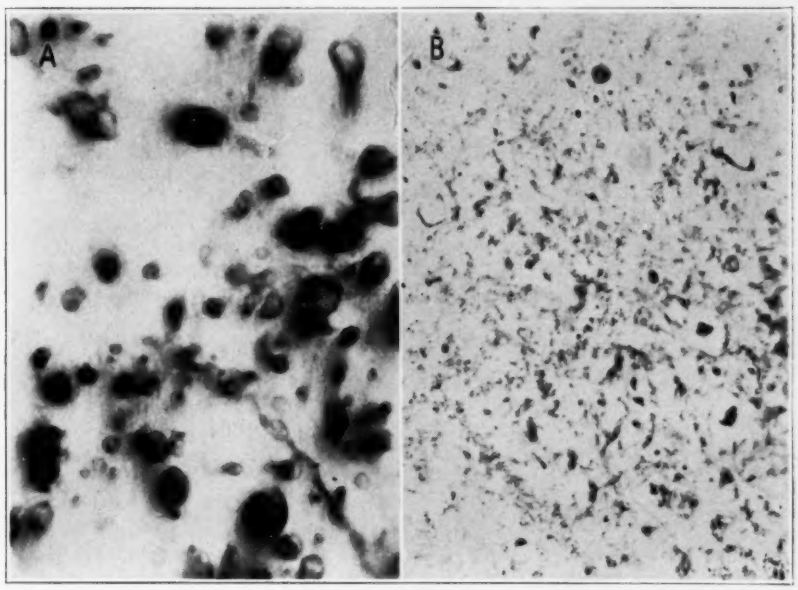


Fig. 4.—Area from the degenerated right anterior pyramidal tract of the spinal cord in the same case as that shown in the preceding figures. × 530. *A*, Weigert-Pal stain; *B*, Bodian stain.

light gray, due to the fact that there is no direct continuity between the various axis-cylinders. The loss of even a considerable number of axis-cylinders may either appear insignificant or fail to make any impression in the low power appearance.

The discrepancy may be even more striking in such lesions as the plaques of multiple sclerosis. High power views of preserved axis-cylinders in plaques reveal not only that their number is far less than the lower power appearance suggests,

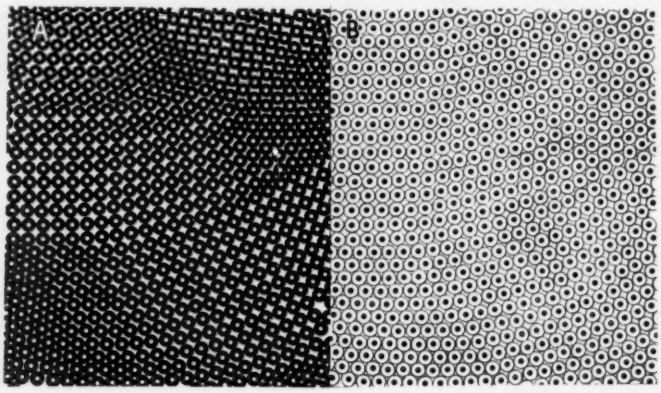


Fig. 5.—Schema of the appearance of fibers cut transversely and stained (*A*) by the Weigert stain and (*B*) by the Bodian stain. The two are drawn to the same scale.

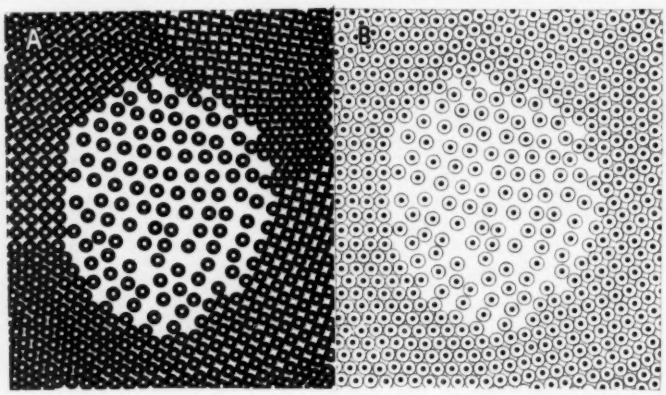


Fig. 6.—Schema of the appearance produced by loss of a large proportion of fibers in a focus, as shown *A* by the Weigert stain and *B* by the Bodian stain. The same number of fibers has been deleted in each instance in exactly corresponding places.

but, in addition, that the remaining axis-cylinders are usually severely damaged, that is, shrunken and attentuated and frequently reduced to threads (fig. 7 *A*) far thinner than axis-cylinders in normal tissue (fig. 7 *B*). This is equally true of incomplete softening due to vascular occlusion. The same phenomenon was found

in experimental scars following transection of meningeal and intracerebral blood vessels in cat brains.[2] More complete reports on all of these matters are in preparation.

This observation may bear on the question whether the damage to the axis-cylinders or that to the myelin sheaths is primary. The classic opinion in regard to multiple sclerosis has been that the damage to the myelin sheaths is primary. From our own experience it appears more likely that the myelin sheaths and the axis-cylinders are damaged simultaneously in sclerotic plaques, foci of softening and other asphyctic lesions, although the axis-cylinders are on the whole slightly more resistant to complete destruction, like the elastic tissue in blood vessels, to which they have interesting microchemical similarities. The close physicochemical interdependence of myelin sheaths and axis-cylinders has been

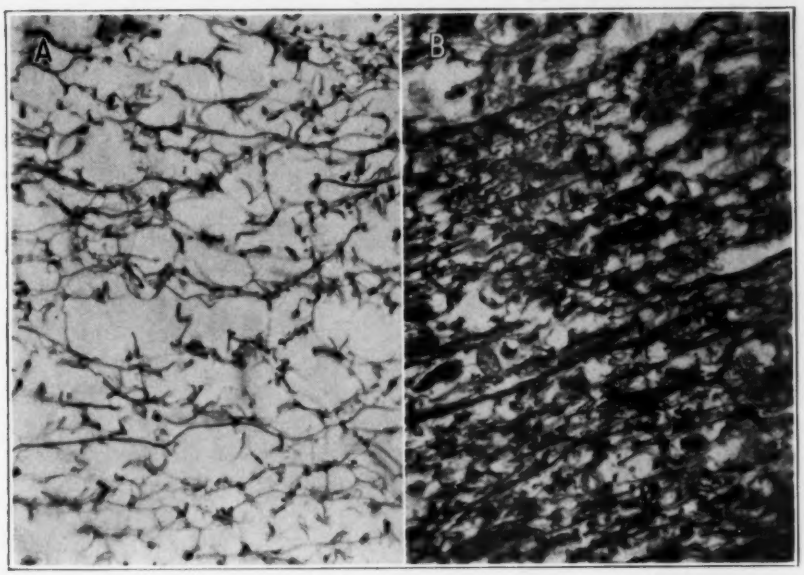


Fig. 7.—*A*, axis-cylinders in a plaque of multiple sclerosis; *B*, axis-cylinders in adjacent normal tissue from the same section as that shown in *A*. × 530. Bodian stain.

described by Spiegel [3] as "zygiosis." In view of recent work by Schmitt and Bear,[4] an alternative possibility may be considered, namely, that

2. Alexander, L., and Newbill, H. P.: Time Determination of Histopathological Changes in the Brain: Experimental Incisions into the Brain with Transection of Meningeal and Intracerebral Blood Vessels in Cats, read before the New England Pathological Society, Boston, Feb. 17, 1938.

3. Spiegel, E. A.: Physikalisch-chemische Untersuchungen am Nervensystem: II. Der Einfluss der Narkotica auf die Anisotropie des Nervenmarks, Arch. f. d. ges. Physiol. **192**:240-254, 1921.

4. Schmitt, F. O., and Bear, R. S.: The Ultrastructure of the Nerve Axon Sheath, Biol. Rev. **14**:27-50, 1939.

damage to the axis-cylinders may be actually primary, though their destruction may be less complete in some cases. These authors have shown by ultramicroscopic and birefractive studies that the transition from the myelinated to the nonmyelinated fibers is gradual and that the degree of birefringence or the presence of myelotropic material is correlated with the diameter of the axon. This suggests that the process of shrinkage and attenuation of an axis-cylinder might be one of the causes of its demyelination.

SUMMARY

The appearance of preservation of the axis-cylinders in certain lesions is frequently an optical illusion and may occur even in lesions due to simple wallerian degeneration. It is emphasized that no assumption of complete or relative preservation of axis-cylinders should be made from the inspection of pathologic specimens without comparative counts of axis-cylinders and of myelin sheaths.

Obituaries

JULIUS WAGNER-JAUREGG, M.D.

EMINENT PSYCHIATRIST AND ORIGINATOR OF THE MALARIA TREATMENT OF DEMENTIA PARALYTICA

1857–1940

Psychiatry has lost one of its great leaders. Dr. Julius Wagner-Jauregg died on Oct. 1, 1940, in his eighty-fourth year.

He was born in Wels, in Upper Austria, on March 7, 1857. His student days were spent at the University of Vienna, where the degree of doctor of medicine was conferred on him in 1880. He began his scientific career in the department of experimental pathology and internal medicine of the University of Vienna. In 1883 he joined the staff of the psychiatric clinic, although he had cherished other plans, which failed to materialize. It was not his original wish to be a psychiatrist, but soon he came to like the new position, because it afforded much time for research.

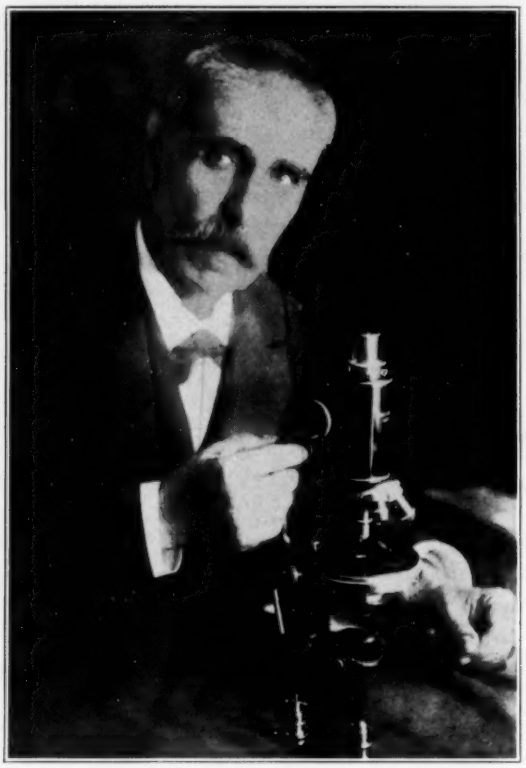
With curious interest he noted the occasional disappearance of mental symptoms in patients who had incidentally become ill with typhoid fever. This observation induced him to make a study of the effects of fever on psychoses. He surmised that such treatment might possibly have merit, and in a publication in 1887 he proposed to produce febrile diseases deliberately as a treatment for psychiatric patients. He ventured to suggest the use of malaria and erysipelas.

Eager to put his proposals into actual practice, he infected several patients with mental disease with a culture of the streptococcus of erysipelas. None of the patients was suffering from dementia paralytica. But neither erysipelas nor fever developed. These experiments had to be discontinued because of his appointment as professor of psychiatry and neurology at the University of Graz (Austria). This position he retained from 1889 to 1893.

When tuberculin was developed in 1890 by Robert Koch, a substance was available with which it was possible to produce fever without resorting to an infectious disease. Wagner-Jauregg then started to treat patients of the psychiatric clinic at Graz with injections of tuberculin. These experiments also had to be stopped temporarily, because tuberculin was soon considered a dangerous preparation.

At this time he was called to Vienna to become the head of the University Hospital for Nervous and Mental Diseases. The vehement

disputes about the use of tuberculin were now subsiding, and its value was gradually recognized. It was in 1894 that he resumed the experimental work with tuberculin fever, using patients with all types of mental conditions. Many therapeutic successes were observed in diseases which fell in diagnostic groups which have a high percentage of spontaneous recoveries. It was therefore difficult to evaluate the effect of this method of treatment. Among patients apparently cured, how-



JULIUS WAGNER-JAUREGG, M.D.
1857-1940

ever, there were a few with dementia paralytica. This was indeed something unusual, and it attracted his attention. Thereafter the main interest of Wagner-Jauregg was focused on patients with dementia paralytica. Several groups of such patients were given tuberculin fever. Then he compared these groups of patients with some who had not been treated. The result was that the tuberculin-treated patients had not only more and better remissions but also longer duration of life. The

injections of tuberculin were combined with mercurial inunctions. In several instances a complete remission was obtained, and the patient was enabled to resume his former occupation.

A report of this work was made in 1909 at the International Medical Congress in Budapest, Hungary. At this period the tuberculin-mercury treatment was the most promising therapy for dementia paralytica. Psychiatrists in general, however, ignored this fact. To be sure, with the tuberculin-mercury treatment relapses were frequent. Wagner-Jauregg searched for more effective means. Although the use of typhoid vaccines was unquestionably an improvement on the earlier methods with tuberculin, lasting remissions were few.

The idea of using malaria for producing fever continued to persist in his mind. He was, however, reluctant to resort to malaria inoculations until the summer of 1917. A wounded and shell-shocked soldier, who was also suffering from tertian malaria, was admitted at that time to the psychiatric clinic. This incident Wagner-Jauregg chose to regard as "a sign of destiny," as he called it. From the cubital vein of this soldier he obtained blood and inoculated 3 patients with dementia paralytica. That was on June 14, 1917. This day marked the beginning of the malaria treatment, which soon spread to every corner of the world.

In 1927 Wagner-Jauregg was awarded the Nobel Prize for his work in the use of malaria fever in the treatment of dementia paralytica. It was the first and up to date the only time that a psychiatrist has been the winner of this prize. In 1938, at a special meeting in New York, an award of $1,000 and a medal were presented to him by the Committee on Research in Syphilis, an American committee. He was an honorary member of the American Psychiatric Association.

In earlier years Wagner-Jauregg made numerous contributions to medical literature on neuropathology and on physiologic and pharmacologic subjects. His excellent judgment in matters of forensic psychiatry was recognized throughout Europe. Cretinism, myxedema and the prevention of goiter were fields which, next to fever therapy, held his lifelong interest.

He reached the age of 70 on March 7, 1927. On that occasion a celebration was held in his honor in the old chapel of the psychiatric clinic of Vienna. In oratorical tributes he was hailed as the conqueror of dementia paralytica. Wagner-Jauregg, however, was the first to protest this, stating that in spite of malaria treatment too many patients with dementia paralytica fill mental disease institutions, although he recognized that many thousands who normally would have been dead had been returned to their families and to normal occupations.

After retirement from his professorship in 1928, he spent much time in the high-ceilinged, old-fashioned study of his home at Landes-

gerichtsstrasse 18, Vienna. He continued to search and to write. Most important to him, in his later years of life, was the prevention of dementia paralytica and in this he saw the real future of the malaria treatment. Occasionally he would come to the clinic and walk through the wards. This clinic now is known as the Wagner-Jauregg Clinic.

Wagner-Jauregg had the ability to distinguish unerringly truths from half-truths and to fix his attention on things of enduring value. He knew how to weigh evidence, whether in the laboratory or at the bedside, and how to assign it to its proper place. Those who had the privilege and good fortune to come into contact with this rare personality could not but feel themselves in the presence of a truly great man.

WALTER L. BRUETSCH, M.D.

ARTHUR STEPHEN HAMILTON, M.D.

1872-1940

Dr. Arthur Stephen Hamilton died at his home in Minneapolis on June 2, 1940. He had been severely incapacitated for nearly five years from the residuals of a series of cerebral vascular accidents.

Dr. Hamilton was born at Wyoming, Iowa, Nov. 28, 1872. He graduated from the University of Iowa and then transferred to the University of Pennsylvania for his medical training, receiving the degree of Doctor of Medicine from that institution in 1897. His course through the medical school represented a period of considerable hardship due to financial stringency, which imposed a limited diet on him and necessitated extracurricular work to supplement his meager funds. The stimulation which he received as a student of Mills and Spiller was undoubtedly a potent factor in the choice of neurology and psychiatry as his specialty. After receiving his medical degree, Hamilton became an assistant physician at the Independence State Hospital in Iowa and held that position until 1904. At Independence he became greatly interested in neuropathology and published numerous papers on the pathology of conditions which at that time had received little attention from microscopists. At Independence he was associated with two other physicians who also were destined to advance knowledge of neurology and psychiatry—Dr. Albert M. Barrett and Dr. Adolf Meyer. While at Independence, he married Dr. Susanna P. Boyle, who was also a member of the state hospital staff; there are no children of their union. In 1904 Dr. Hamilton moved to Minneapolis, entering the practice of neurology and psychiatry and receiving an appointment as instructor in neuropathology at the University of Minnesota. He advanced through the academic ranks to a full professorship, which he received in 1916. In 1912 he was made director of the Division of Nervous and Mental Diseases and was professor and director until the onset of his terminal illness, in 1935. Two extended study trips abroad gave him familiarity with the clinical methods of Germany and England, especially the latter; these he applied in his practice and emphasized in his teaching.

Dr. Hamilton served in 1918 and 1919 as captain and major in the United States Army, during the World War.

Hamilton was considered by his students to be an unusually systematic and lucid teacher, both in the lecture room and at the bedside. His breadth of knowledge, clear analytic thinking, careful technic, gentleness with patients and consideration for the younger colleagues' opinions constituted in him the nearly ideal combination for an adviser and preceptor of the more advanced students.

Though rather reserved and dignified, he was never austere or supercilious, but was approachable, friendly and rarely ruffled. His appreciation of the social implications of neurology and psychiatry drew

him into active participation in civic affairs, so that he was frequently consulted on matters involving the welfare of the community and the state. Preferring the pursuits of practice, teaching and investigation, he nevertheless was an active participant in numerous national and local

ARTHUR STEPHEN HAMILTON, M.D.
1872-1940

societies; he was a past president of the Central Neuropsychiatric Association and former chairman of the Section on Nervous and Mental Diseases of the American Medical Association.

Minnesota and its environs have benefited from the presence of Arthur Hamilton. His many friends grieve over his passing.

J. C. McKinley, M.D.

Abstracts from Current Literature

Psychiatry and Psychopathology

ON A FORM OF DEFENSE. SIGMUND PFEIFER, Psychoanalyt. Quart. **9**:108, 1940.

Pfeifer describes a form of defense met with in certain cases in which the clinical picture resembles a perversion, usually masochistic; i. e., portions of libido are admitted to consciousness which in other neuroses would be repressed. This happens because of a peculiar psychic reaction to anxiety. It is no longer a signal introducing defensive measures, but is a danger in itself. The patients defend themselves against the danger of anxiety by trying to fuse it with libido; i. e., they ward off the anxiety by inducing an erotic sensation. The anxiety which is feared is a castration anxiety consisting of two parts: (1) a fear of losing the penis and (2) a fear of never being able to experience erotic sensations again. This defense phenomenon may appear in the field of object love, but usually operates most in the field of narcissism.

Psychologically, such patients must possess an immoderate degree of self love or must make immoderate demands for love on others in order to keep themselves free from anxiety. Metapsychologically, they are exposed to two dangers: (1) their own increased libidinal excitation for the purpose of avoiding anxiety, which increase is akin to a threat of castration, and (2) fear of the danger of a relative decrease in the amount of excitation lest there should be not enough libido to ward off anxiety.

Why these patients are unable to tolerate even enough anxiety to set ordinary defensive measures in action is unknown. Their form of defense, the attempt to ward off anxiety by neutralizing it with libido, which they regard as a manifestation of the death instinct and therefore dangerous, is exactly the same as the primitive defense against the death instinct by fusing it with libido.

PEARSON, Philadelphia.

THE PRODUCTION OF "EXPERIMENTAL NEUROSIS" IN THE WHITE RAT. S. W. COOK, Psychosom. Med. **1**:293 (April) 1939.

Cook utilized four experimental procedures in an attempt to produce relatively permanent behavior disorders in rats similar to those previously observed in other animals. The procedures were designed to present the animal with stimuli to conflicting and mutually antagonistic responses. In the earlier experimental procedures it was observed that there was a tendency for rats to utilize agitated escape responses to relieve the strain of the experimental situation. This hypothesis was then tested by a specially designed experiment in which the same stimulus situation was associated with forced limitation of the rat's activity. In contrast with the negative results of the earlier experimental procedures, half of the animals subjected to limitation of activity showed persistent maladaptive behavior.

In the experimental situation which proved successful, the rats were strapped to a stand so that the only significant limb movement possible was a flexion of the right foreleg. Under these conditions such a flexion movement was either rewarded with food or punished with an electric shock. Stress was experienced by the rats when: (1) they were required to delay flexion until they received a bright light stimulus; (2) they were required to make a difficult discrimination between a bright light stimulus which permitted flexion and a dim light stimulus which prohibited flexion. In such a situation the stresses consisted of a conflict between the neural processes of excitation and inhibition effecting the same response. In this respect the experimental situation which proved successful with the rats is comparable with the situations in which an "experimental neurosis"

had been produced in other animal species. However, no common pattern of behavior disturbance was observed in the 3 affected rats. Noteworthy was the fact that the onset of symptoms in the rats was gradual, whereas in other animals the onset had been reported as usually rapid.

SCHLEZINGER, Philadelphia.

ANOREXIA NERVOSA WITH PSYCHIATRIC OBSERVATIONS. L. RAHMAN, H. B. RICHARDSON and H. S. RIPLEY, Psychosom. Med. **1**:335 (July) 1939.

Rahman, Richardson and Ripley made a detailed physical and psychiatric investigation of 12 patients with the syndrome of anorexia nervosa. All were discovered to have a psychoneurosis associated with endocrine dysfunction which became manifest near puberty. In some patients there were conspicuous obsessive, compulsive, anxiety and depressive features. In others schizoid features were prominent. In the cases of milder form malnutrition usually resulted from failure to eat due to an anxiety reaction accompanied by anorexia. In cases of the more severe disturbance hunger was overcome by voluntary dieting. Significant physical findings consisted of emaciation, dry and scaly skin, cold and cyanotic extremities, amenorrhea, atrophic vaginal epithelium, subnormal temperature, bradycardia and low blood pressure. The personality features which might be considered characteristic included stubbornness, meticulousness, parsimoniousness, ambitiousness, seclusiveness, dependence on others and difficulty in making friends. The patients frequently disclosed avoidance of normal sexual relationships. Often the patients in early life had been exposed to excessive parental interest in gastrointestinal functions. In the treatment of these patients the authors recommend a regulated, but flexible, regimen. They conclude that endocrine therapy has been of no definite value. Psychotherapy is emphasized and is based on a psychodynamic study of the personality, with reeducation and encouragement.

SCHLEZINGER, Philadelphia.

PERSONALITY FACTORS IN NEURODERMITE. N. W. ACKERMAN, Psychosom. Med. **1**:366 (July) 1939.

Ackerman considers the probable psychodynamic factors present in the case of a girl aged 14 who had a chronic ailment of the skin since the age of 2 years. The patient evidenced marked disturbance in character, in which aggressiveness, rebelliousness, vindictiveness and sexual promiscuity were conspicuous features. The author concludes that the more or less constant tendency to excoriate the skin is chiefly an expression of self-destructive impulses arising from the patient's unconscious conviction that she had caused her mother's death.

SCHLEZINGER, Philadelphia.

THE COMMON CAUSE IN THE FUNCTIONAL INSANITIES. T. C. GRAVES, Brit. M. J. **1**:608 (April 13) 1940.

Graves's premise is that patients with functional psychoses are physically infirm and that there is a common cause for the mental and the physical illness. He admits the importance of a psychologic factor in these cases. From a physiologic standpoint, mental illnesses may be the result of biologic maladjustment, nutritional deficiencies or sensory deficiency (congenital or acquired). It has been shown that infection affects the autonomic endocrine mechanism, with clinical manifestations in vascular and cutaneous changes and the symptom of fear. It is generally agreed, but extremely difficult to demonstrate, that there is a definite pathologic state in these cases of mental disease. Physical ill health has often been observed preliminary to the psychotic state. It has long been known that apparent cessation of a purulent discharge may be followed by the onset of mental symptoms.

The author considers a chronic infective process as the link between the psychotic and the bodily disease and calls this the "common cause." He indicates

that the basal cause may exist without the accompaniment of either psychotic or somatic disease, but that it is persistent and progressive. He believes that this chronic infective process originates as a transmissible familial infection, but that it usually first appears as a residuum of an acute infective process, during which the patient may have exhibited mental symptoms. He states that the chronic infective process is to chronic mental disease what the acute infective process is to acute delirium. As illustrative of his explanation of mental illness, he reports a case in which psychologic, physiologic and pathologic factors were demonstrable, but there was also a "common cause," namely, chronic infection of the sphenoid sinus. Recovery followed surgical treatment.

ECHOLS, New Orleans.

INCIDENCE OF PSYCHOSES AMONG CHILDREN BOTH OF WHOSE PARENTS HAD AFFECTIVE PSYCHOSES. BRUNO SCHULZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:311 (April) 1940.

Schulz studied 55 married couples both of whom had some type of affective psychosis. Only couples were chosen who had at least 1 child 20 years of age or more. There were 213 children, with 1 pair of twins. The social level of the parents was definitely higher than that of another series in which both parents were schizophrenic or in which only one of the parents had an affective psychosis. The incidence of psychoses among the children was lowest in the group in which at least one of the parents had an affective psychosis in some way related to age (involuntional melancholia)—7 per cent with manic-depressive psychosis and 4 per cent with schizophrenia. Among the children of parents one of whom at least showed schizophrenic features the incidence of psychoses was definitely higher—30 per cent with manic-depressive psychosis and 7 per cent with schizophrenia. The highest incidence was in the children of parents both of whom had affective psychoses—37 per cent were manic-depressive and 13 per cent schizophrenic. The incidence of psychoses, exclusive of those related to age, was 28 per cent for manic-depressive psychosis and 12 per cent for schizophrenia. Twenty-one of the 55 couples had no psychotic children.

The incidence of psychoses in the children of parents both of whom had affective psychoses is definitely higher than that encountered in the children of parents only one of whom had an affective psychosis. These facts reemphasize the probable role of genetic factors in the pathogenesis of these mental diseases. The relatively large number of schizophrenic children of manic-depressive parents is noteworthy. Manic-depressive children of schizophrenic parents, on the other hand, are rare.

SAVITSKY, New York.

Diseases of the Brain

NEUROLOGIC COMPLICATIONS OF INFECTIONS OF TEMPORAL BONE AND PARANASAL SINUSES. JOSEPH C. YASKIN, Arch. Otolaryng. **30**:157 (Aug.) 1939.

Yaskin reports the neurologic complications of infections of the temporal bone and paranasal sinuses in 36 cases occurring during a practice of twenty years. In the majority of cases the diagnosis was confirmed by operation or autopsy. Among the predominantly meningitic reactions are pachymeningitis externa and extradural abscess, pachymeningitis interna and subdural abscess, superscribed leptomeningitis, protective meningitis, bacterial leptomeningitis, meningismus and arachnoiditis. Pachymeningitis externa and extradural abscess occur more often in the cases of chronic infection, especially of the frontal sinuses, the most frequent cause of which is osteomyelitis. Headache and labyrinthine signs may help to locate the area involved. Treatment is surgical. Pachymeningitis interna and subdural abscess are less frequent and more difficult to diagnose. They occur in more acute conditions, usually by extension from an area of pachymeningitis externa. Protective or aseptic meningitis is accompanied by the typical signs of meningitis, including increase of cells in the spinal fluid without the presence of bacteria. In the majority of cases in which this diagnosis was made early, the

meningitis was proved by subsequent studies to be bacterial. In a large majority of the cases bacterial leptomeningitis was due to complications involving the nose and throat, and especially the ear. Finding bacteria is essential for diagnosis, but chemical analysis of the spinal fluid may suggest this complication.

Abscess of the brain is most frequently due to disease of the temporal bone. It occurs most often in the temporal region. Sixteen rhinogenic abscesses of the brain were all in the frontal lobe. Abscesses may be classified according to their location in the brain and the rapidity of their development. Of the 23 abscesses of the temporal lobe, 8 were acute and 15 chronic. Of the 17 patients with fatal abscesses, 11 died of terminal meningitis, 4 of cerebral compression and 3 of septicemia. An initial chill was not observed; headache was present in all cases, dizziness in 8, early vomiting in 14 and early or late vomiting in 18. In 2 cases it was so conspicuous as to obscure the whole picture. Mental changes were observed in 20 cases. The temperature was normal in the majority of cases unless the abscess was associated with other processes. The pulse was slow in 19 of the 23 cases. There was papilledema in 8 of the 18 cases in which it was looked for. Contralateral hemianopic defects were seen in 11 of 17 cases. Jacksonian convulsions occurred in 1 of the 23 cases and generalized convulsions in 2. The spinal fluid pressure was elevated in 7 of 17 cases. The cell content of the spinal fluid, determined in 15 cases, showed a slight increase in 6. Vestibular studies helped to diagnose lesions of the posterior fossa and occasionally to lateralize the lesion. Three of the 17 patients with abscesses of the frontal lobe survived. In 14 cases the abscess originated in the frontal sinus; in 4 it resulted from diving, in 3 there was clinical and roentgen evidence of osteomyelitis of the frontal bone, in 2 the abscess followed trauma and in 5 it was classified as due to chronic frontal sinusitis. In 5 of the cases sinuses other than the frontal were affected. In 1 of the 17 cases the abscess arose from ethmoiditis, in 1 from sphenoethmoid osteomyelitis and in 1 from chronic disease of the temporal bone. In 1 case the abscess of the frontal lobe was contralateral to the sinus. In all the cases of abscess of the frontal lobe there was a history of a chill or septic process; headache was prominent in all, and dizziness and vomiting in 6. The mental state varied. There was a slight rise in temperature in all 17 cases; a slow pulse was recorded in 5 cases, edema of the orbital region in 5, exophthalmos in 6 and papilledema in 9. Hemiparesis, of variable degree, was observed in 7 cases, mixed aphasia in 1 and generalized or jacksonian convulsions in 4. In 7 of the 9 cases in which it was recorded the spinal fluid pressure was elevated, with increase in cells. Roentgenograms were of no value except in 1 case, in which a pineal shift localized the lesion contralateral to the sinal infection. Cerebellar abscesses were found in 4 cases. There was 1 recovery. In 3 of the cases clinical evidence of meningeal irritation appeared. In all cases there was increased intracranial pressure.

HUNTER, Philadelphia.

ANATOMIC, CLINICAL AND GENETIC INVESTIGATIONS ON PSEUDOSCLEROSIS. H. STADLER, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:583 (Feb.) 1939.

Unusual cells, resembling closely the Alzheimer glia cell of the brain, were observed in the livers of patients with pseudosclerosis. Glycogen was found in these cells, even in livers preserved for a long time in formaldehyde. Glycogen could not be demonstrated so readily in the Alzheimer glia cells. The presence of iron in Alzheimer glia cells points to the probable functional activity of these cells. In 3 cases severe changes were observed in the dentate nuclei—destruction of ganglion cells, neuronophagia, glia rosettes and lymphocytic infiltration. These changes were similar to those reported by Spielmeyer in cases of typhus fever. In 1 case there were few glycogen-laden cells in the liver, and at the same time few Alzheimer glia cells.

Eighteen cases, occurring in ten families, were studied clinically. There was a familial incidence in five families. There was also a significant number of cases of consanguinity. Pseudosclerosis was encountered only in siblings in the same

family. It was not found in parents or in collateral relatives. There was no evidence of sex linkage. In 2 cases an increased permeability quotient (more than 1) for chlorides was found. The normal quotient is usually between 0.8 and 0.9, and is constant. Stadler could not confirm the observation of Kehrer that marked leukopenia has diagnostic significance. The lowest white cell count in this series was 4,800. In 2 cases there were abnormal colloidal gold curves. The occasional occurrence of coma in this disease is noted. These comatose states last for variable periods. In 2 cases, both in the same family, the author noted eosinophilia and considered it to be related to the disease process. Mental changes were noted in all the patients. In the younger patients, in whom the disease began during or before puberty, physical and mental immaturity was frequent. Six of the 13 younger patients were mentally defective. This intellectual retardation is considered to be due to the organic process in the brain accompanying pseudosclerosis. It is not coincidental. The importance of not judging the intellectual level of these patients by their appearance is emphasized. They may look dull, and even demented, because of the hypomimia, rigidity and lack of spontaneity almost always present in this disease. In the older patients all varieties of mental changes were observed, as in patients with other organic diseases of the brain. In both groups, perhaps somewhat more prominent in the younger, one finds irritability, slowing of movement and thinking, sensitivity, depressive episodes, and at times even paranoid tendencies. One patient presented definite catatonic features and another a definite manic picture, which was attributed to the existence of a cyclothymic predisposition.

The author believes that pseudosclerosis is fundamentally a hereditary defect in carbohydrate metabolism.

SAVITSKY, New York.

CLINICAL STUDY OF INVOLVEMENT OF THE NERVOUS SYSTEM IN CONGENITAL SYPHILIS. HERMAN SCHULTE, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:250 (March) 1940.

Schulte found congenital syphilis in 120 (2.5 per cent) of 4,715 children admitted to a service for child psychiatry. These children were observed from 1926 to 1937, inclusive. Mental deficiency was present in 78 (65 per cent); in 59 per cent the defect was congenital and in 6 per cent it became evident during the first few years of life. Fourteen patients were idiots. Six of the idiots had positive serologic reactions of the blood alone, 1 of the spinal fluid alone and 5 of both the blood and the spinal fluid. Two patients with entirely negative serologic reactions had had adequate treatment in the first year of life, when positive serologic reactions were found. Six patients had microcephaly, 7 convulsions, 2 optic atrophy and 5 spastic tetraplegia. Five children had a family history of mental retardation, criminality and alcoholism.

Less pronounced forms of mental deficiency are more characteristic of congenital syphilis. There were 35 imbeciles and 13 children with borderline intelligence. Only 9 of the 35 imbeciles had a good family history. Convulsions were noted in only 5; the serologic reaction of the blood was positive and that of the spinal fluid was negative in 18 cases, that of the spinal fluid was positive and that of the blood was negative in 2 cases; the reactions of both the blood and the spinal fluid were positive in 7 cases and negative in 8 cases. In addition to lymphadenopathy, pallor, Hutchinson teeth, rhagades and other evidence of syphilis, these 35 imbecile children showed the following neurologic signs: macrocephalus, 1; meningocele, 1; external hydrocephalus, 2; adiposogenital dystrophy, 2; signs of involvement of the pyramidal tract, 8; weakness of the facial nerves, 6; weakness of the hypoglossal nerve, 2; hypomimia, 3, and hypotonia, 4. Anisocoria was found in 4 cases, irregular pupils in 4 cases, sluggish pupillary reactions to light in 3 cases and complete pupillary rigidity in 1 case. Nerve deafness was found in 1 case, optic atrophy in 1 case, nystagmus in 2 cases and isolated palsy of the trochlear nerve in 2 cases.

There were 13 children with borderline mentality, 5 of whom showed significant character defects. In 8 the intellectual defect dominated the clinical

picture. In 3 there was marked physical infantilism. Three patients had had convulsions in early childhood. In 6 cases serologic reactions were negative, with a history of a positive serologic reaction in 2. In 6 cases only the reaction of the blood and in 1 the reactions of the blood and the spinal fluid were positive. There were 8 children (6.6 per cent) with severe character defects and normal intelligence. Six of these children had defective family histories; 5 showed hyperkinesis, somnambulism, pavor nocturnus and irritability. Of the 5 children, 4 had a positive serologic reaction of the blood; the child with a negative serologic reaction showed pleocytosis and increased protein in the spinal fluid; 2 of the other 3 patients had negative serologic findings. The character defects were mainly in the nature of lying, stealing, attacks of rage and impulsive behavior. There were 4 patients who showed the type of restless, impulsive behavior characteristic of chronic encephalitis in children.

Four children were admitted for neurologic disorders without mental symptoms, evidence of retardation or a character defect; 1 of these had spastic tetraplegia, the second hemiplegia with onset during the fourth week of life, the third spastic paraparesis beginning in the third year and the fourth an extrapyramidal dyskinetic syndrome present since birth. Three patients were admitted because of mental symptoms accompanying severe disturbances of the special senses—1 with blindness due to keratitis and 2 with deafness.

Convulsive seizures were noted in 23 of the 120 cases. In 16 cases convulsions were most prominent in the clinical picture. Of these 16, intellectual defects were evident after the attacks appeared in 10; the serologic reactions were entirely negative in 4; there were a positive reaction of the blood and a negative reaction of the spinal fluid in 4, a positive reaction of the spinal fluid and a negative reaction of the blood in 4 and positive reactions of the blood and spinal fluid in 4. There were spastic hemiparesis in 2 cases, flaccid hemiparesis in 1 case, crossed spastic paresis of the left upper and right lower limb in 1 case and spastic crural monoparesis of the right lower limb in another. There were pupillary anomalies in 6 cases—anisocoria in 3, irregularity in 4, abnormal reaction to light in 4 and inordinate dilatation in 2 cases. Keratitis alone was present in 1 case, keratitis with chorioretinitis in 1, chorioretinitis alone in 3 and chorioretinitis with optic neuritis in 1. The onset of convulsions was most often in the first year (4 cases). In 6 cases the convulsions appeared for the first time between the tenth and the twelfth year. In 7 cases the attacks were of grand mal and in 7 of jacksonian type, and in 2 there were frequent petit mal seizures. In 2 cases the attacks were tonic. In 2 cases there were episodic cloudy states in addition to the convulsions. In all cases some degree of intellectual retardation and enfeeblement existed, in addition to more or less severe changes in behavior.

Juvenile dementia paralytica was encountered in 14 patients, or in 1.5 to 2 per cent of all the congenital syphilitic children in this series. There were 9 boys and 5 girls. Seven of the children with dementia paralytica were retarded mentally before the onset of the paresis; 6 were normal, and no information was available about the premorbid intellectual status of 1. In about half the cases the time of onset of psychotic behavior was more or less clear. The age of onset was between the eighth and the fourteenth year in two thirds of the children. The mode of onset varied greatly—increasing loss of interest, failure in school work, memory defect, speech disturbance, hypersensitivity, silliness, anxiety and attacks of screaming; character defects, such as lying, destructiveness and profanity, were observed. In some cases the onset was with somatic complaints, such as headache, dizziness, insomnia, somnolence, loss of weight, amenorrhea or unexplained sudden rise in temperature. In 1 case the illness began with gradual spastic paresis of one lower limb; in another the patient complained of intolerable sensations of heat at night. Convulsions were noted in 4 cases, and were confined to the right upper limb in 1 case. Eleven of the children were underweight; 1 showed a Fröhlich habitus, and only 2 could be considered to be normally developed. The usual syphilitic stigmas were found as frequently as in the other groups. In 7

cases there was definite hypogenitalism. Four of the children with dementia paralytica showed marked acrocyanosis; 2, status marmoratus involving the limbs, and many of the others, sialorrhea, hyperhidrosis and dermatographism. In 3 cases the thyroid gland was enlarged; in 1 of these cases there was thyreotoxicosis. Pupillary changes were found in all but 2 cases—there were anisocoria in 10 and irregularity in 6; the pupils were moderately dilated in all cases; miosis was not observed; marked mydriasis was seen in 3 cases, and in 9 cases the pupils did not react to light. Two of the patients showed optic atrophy, 1 palsy of the abducens nerve and 2 paralyses of the hypoglossal and facial nerves. Hyperreflexia was noted in 8 cases and areflexia, with signs of lesions in the posterior columns, in only 1. Six of the children had the dysarthria characteristic of dementia paralytica. Only 1 child had no positive neurologic findings. The mental pictures varied. Dulness and apathy, with marked enfeeblement and repetition of senseless phrases, were seen in 4 cases; in 1 case there were attacks of destructive and assaultive behavior; in 4 cases there was marked anxiety in strange surroundings; in 2 euphoria with spontaneous overproductivity was noted; in 3 repeated attacks of yelling and screaming occurred, and in 2 marked emotional lability was most prominent. The results of treatment were entirely unsatisfactory.

SAVITSKY, New York.

FURTHER STUDY ON MODE OF EXTENSION OF HYPOPHYSIAL ADENOMA. P. VOSSKÜHLER, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:444 (April) 1940.

Vosskühler reports 3 cases illustrating the variations in extracapsular extension of hypophysial adenoma. In the first case there was extension into the medial aspect of the temporal lobe and the sphenoid sinus. The clinical picture was not unusual and was typical of a chromophobic adenoma. A woman aged 33 complained of progressive diminution of vision for two years, with recent severe occipital headache. Amenorrhea had been present since the age of 26, with hypotrichosis in the axillary and pubic regions. The hair on the head was also sparse. There were bitemporal hemianopia and erosion of the sella and clinoid processes.

In the second case there were involvement of the temporal lobe and severe compression of the pons. The tumor was large, the size of a fist, and extended anteriorly to the posterior portion of the orbital surface of the left frontal lobe. This patient was a girl aged 15 who had complained of diminution of vision in the left eye for three years. There had been ptosis of the left eyelid for one year. There was evidence of intellectual enfeeblement, with occasional bouts of nausea and vomiting. The patient looked undernourished and pale, but presented no definite features of endocrine disturbance. The pupillary reactions on the right side were brisk. The right abdominal reflexes were not elicited; there were ankle clonus on the right, weakness of the right side of the face, a positive Babinski sign on the right and hemiparesis with hyperreflexia on the right side.

The third case was that of a man aged 26 in which the hypophysial adenoma grew into the temporal lobe, filling the inferior horn. The tumor became cystic and also extended anteriorly into the sphenoid sinus and posteriorly toward the clivus, causing considerable compression and distortion of the brain stem. The clinical picture was that of increasingly severe headache on the right side, occasional attacks of trigeminal pain, bilateral papilledema and left temporal (quadrantic?) hemianopia. There were exophthalmos of the right eye and destruction of the sella.

SAVITSKY, New York.

PROGNOSIS IN EPIDEMIC ENCEPHALITIS. H. J. USTVEDT, Norsk med. (Norsk mag. f. laegevidensk.) **6**:997 (June 1) 1940.

Ustvedt says that of the 107 patients with lethargic encephalitis treated from 1919 to 1934 by von Economo, 16 per cent died in the acute stage. Of the surviving 90, 87 were followed for from one to nineteen years, 15 of them for from

fifteen to nineteen years. Thirty were fully capable of work and without symptoms, 10 were capable of work but had slight symptoms possibly attributable to the encephalitis, and 20 were capable of work but had certain symptoms, in some cases troublesome. In all, 60 were able to work. Of the 20 with chronic encephalitis, 11 died. The longest interval between the acute stage and new symptoms was eight years. The author says that there are far fewer cases of lethargic encephalitis in Norway than in most European countries and that the immediate mortality seems to have been moderate; follow-up examination with respect to ability to work shows conditions far more favorable than might be expected.

J. A. M. A.

Vegetative and Endocrine Systems

SURGICAL INTERVENTION ON THE SYMPATHETIC NERVOUS SYSTEM FOR PERIPHERAL VASCULAR DISEASE. R. H. SMITHWICK, Arch. Surg. **40**:286 (Feb.) 1940.

Smithwick states that if in a given case impaired blood flow to the extremity is entirely a question of vascular spasm, as in the early stages of Raynaud's disease, sympathectomy will yield its most brilliant result. By contrast, if the vascular insufficiency is the result of chronic obliterative vascular disease, as in advanced arteriosclerosis with associated diabetes, sympathectomy will not be helpful. Many patients, however, suffer from a lesion which is both obliterative and vasospastic, in which case sympathectomy may be helpful. Thromboangiitis obliterans is representative of such a lesion.

Although the primary effect of sympathectomy is probably largely the result of vasomotor paralysis, another factor must be considered. Sympathectomy results in sudomotor paralysis, in addition to vasomotor paralysis. A portion of the effect on the periphery is therefore due to inactivation of the sweat glands.

Vasoconstriction can be reflexly inhibited by warming the trunk or by immersion of the opposite extremities in warm water. Vasoconstriction can also be inhibited by induction of fever by intravenous injection of foreign protein (typhoid vaccine). The resulting rise in surface temperature of the extremity makes it possible to estimate the vasomotor index. All three of these methods have been used extensively. Vasoconstriction can be eliminated also by blocking the efferent vasomotor pathway with procaine hydrochloride. This test perhaps provides a better index of the result to be expected from sympathectomy because the sudomotor pathway is also temporarily interrupted. For the hand, the ulnar nerve is most frequently blocked at the elbow. The foot may be temporarily denervated by procaine hydrochloride block of the posterior tibial nerve at the ankle and of the common peroneal nerve just below the head of the fibula.

In all of the tests mentioned, the increase in blood flow is indirectly measured by the rise in surface temperature of the tip of a finger or toe. In the presence of purely vasospastic disorders this increase will amount to as much as 25 F. If obliterative vascular disease is the predominating factor, there may be little or no rise in surface temperature. If a combination of spasm and obliteration exists, changes in temperature of from 5 to 15 F. are common. Other indirect methods of estimating increased blood flow after inhibition of sympathetic influence are utilized. The finger or toe plethysmograph is a satisfactory and sensitive apparatus. Changes in blood flow may also be quantitated by the hand plethysmograph. The photoelectric cell offers a sensitive method of studying the effect of vasoconstriction. A study of cutaneous resistance as an index of sweat gland activity is helpful in estimating activity of the sympathetic nervous system before and after operation. All of the forms of study mentioned have been utilized. The simplest and most practical is peripheral nerve block. Of the other tests, the study of reflex vascular response by the photoelectric cell method and the study of changes in cutaneous resistance by the Wheatstone bridge and the

psychogalvanic reflex have proved most valuable. These two studies have enabled the author to separate activity of the sympathetic nervous system into its vasomotor and its sudomotor components.

When complete sympathectomy has been accomplished, the level of cutaneous resistance is high and vasomotor and sweat gland activity are abolished. When the operation is only partly effective, the level of the surface temperature is but little changed, and peripheral nerve block will result in a marked rise in cutaneous temperature. The level of cutaneous resistance will be low, reflex sweat gland activity will be present, reflex vasomotor responses will persist and sensitivity to epinephrine will not appear.

GRANT, Philadelphia.

MASCULINIZING AND NON-MASCULINIZING CARCINOMATA OF THE CORTEX OF THE ADRENAL GLAND. T. H. MCGAVACK, Endocrinology **26**:396 (March) 1940.

The problem of the cause of the essential lesion in pituitary basophilism has not yet been satisfactorily solved, and the clinical analysis and conclusions in many cases of this condition leave much to be desired. Numerous instances of the syndrome associated with carcinoma of the adrenal cortex are recorded in the literature. With this in mind, McGavack reports 6 cases of carcinoma of the cortex of the adrenal gland, in 4 of which the diagnosis was confirmed by autopsy and in 2 by operation and biopsy. Adrenal neoplasm associated with masculinization was found in 3 patients, all females, 2 of whom presented the adrenogenital syndrome with late evidences of chronic adrenal insufficiency, while the third had a condition more or less typical of pituitary basophilism. In the case of the only male in the group an abdominal mass and cachexia were the sole features of the disease. Of the remaining 2 patients, both females, Addison's disease developed in 1 prior to death, while in the other there was maintained a state of low grade sepsis for at least five months before death; the only features which the last 2 patients presented in common with the others were tumor of the adrenal cortex and absence of virilism.

The author presents and analyzes quantitative hormonal studies of the urine of 18 patients, with records of the content of estrogen, the gonadotropic factor of the anterior lobe of the pituitary gland and the "androgenic or androgenic-like materials." High estrogen values were obtained only in cases of carcinoma of the adrenal gland, while increased responses to the bitterling test were present in the cases of hyperplasia of the adrenal cortex.

PALMER, Philadelphia.

SEX HORMONE STUDIES IN MALE HOMOSEXUALITY. S. J. GLASS, H. J. DEUEL and C. A. WRIGHT, Endocrinology **26**:590 (April) 1940.

Seventeen homosexual men were studied for the urinary output of estrogen and androgen. Androgens were determined quantitatively by a modified capon technic and by a colorimetric test. The majority of tests, however, were made by the latter method. The values were expressed in international units of androgen (androsterone) per day. The estrogens were determined by the spayed adult rat method and were expressed quantitatively in micrograms of estrogen per day. Numerous specimens covering varying periods were studied. The androgen-estrogen ratios obtained for the homosexual patients were substantially lower than the ratios obtained for the 31 normal control subjects. The estrogen values were uniformly higher and the androgen values varied somewhat, but the differences were less striking. The urinary output of homosexual persons was also subjected to assay of the gonadotropic factor by the Zondek alcohol precipitation method; it failed to show any significant values. In the face of such suggestive hormonal differences in the androgen-estrogen ratios, the authors believe that there is some indication of a biologic mechanism in male homosexuality.

PALMER, Philadelphia.

BILATERAL LOCALIZED LESIONS IN THE HYPOTHALAMUS WITH COMPLETE DESTRUCTION OF THE NEUROHYPOPHYSIS IN A PITUITARY DWARF WITH SEVERE PERMANENT DIABETES INSIPIDUS. A. B. BAKER and C. B. CRAFT, Endocrinology **26**:801 (May) 1940.

Baker and Craft report in detail a case of pituitary infantilism, with severe permanent diabetes insipidus, in a girl aged 18. Postmortem examination revealed bilateral localized lesions in the hypothalamus, limited almost entirely to the region of the supraoptic nuclei. The case is of special interest because of the isolated nature and bilateral location of the lesions; in the experimental animal it is almost impossible to produce such localized lesions because of the mechanical difficulties encountered in limiting the destructive process to the small, relatively inaccessible regions of the hypothalamus. The most striking pathologic changes consisted of extensive areas of demyelination and tissue destruction, bilaterally located within the hypothalamus and limited almost exclusively to the regions superior to and around the lateral aspects of the optic chiasm. The supraoptic nuclei were completely destroyed, and the pituitary gland was so extensively involved that no normal tissue of the posterior lobe could be identified; it was estimated that only about one sixth of the normal number of cells of the anterior lobe remained.

Correlating these remarkable pathologic observations with the anatomic aspects of the case, the authors point out the following observations which seem to confirm the previous work of others regarding the functional importance of the nerve tracts and nuclei of this region: (*a*) The paraventricular nucleus probably has most of its neuronal connections with the supraoptic nucleus, and hence undergoes severe atrophy on injury to the latter. (*b*) Only a very small amount of functioning parenchyma of the anterior lobe of the pituitary is necessary to maintain severe and permanent diabetes insipidus after destruction of the posterior lobe. In the case presented only about one sixth of the normal number of cells of the anterior lobe remained. (*c*) Pituitary dwarfism, while usually due to pressure on the eosinophilic cells of the anterior lobe of the pituitary or to an idiopathic deficiency or arrested development, may also be the result of secondary fibrosis following a primary destructive lesion.

PALMER, Philadelphia.

DIFFERENTIAL DIAGNOSIS OF BASOPHILISM AND ALLIED CONDITIONS. I. DORFMAN, M. WILSON and J. P. PETERS, Endocrinology **27**:1 (July) 1940.

Dorfman, Wilson and Peters present a scheme for the clinical differentiation of basophilism, corticoadrenalism and arrhenoblastoma. The manifestations of these syndromes have been tabulated under three headings: disorders of habitus and circulation, disorders of metabolic function and disorders of general development and of sexual development and function. Only disturbances to which a definite significance can be attached have been included in the tabulation. In disorders of general habitus and circulation, basophilic and corticoadrenal syndromes appear to be indistinguishable, at least in adults. The disturbances of metabolism, diminished carbohydrate tolerance and decalcification of the bones, have been found to be present as frequently in corticoadrenalism as in basophilism. They are not seen with arrhenoblastoma, and hence are valuable diagnostic points in the differentiation of the latter. The same applies to circulatory disturbances.

True virilism seems to occur only with tumors and hyperplasia of the adrenal cortex and with arrhenoblastoma. In the former conditions the urine has been found to contain abnormally large amounts of materials having androgenic activity. Precocious sexual development and abnormally early fusion in the epiphyses occur if the corticoadrenalism appears before growth is completed, whereas in basophilism there is retardation of growth and epiphysial union. In all the cases analyzed the urinary estrogenic activity was found to be within normal limits.

PALMER, Philadelphia.

THE DIFFERENTIAL DIAGNOSIS OF CUSHING'S SYNDROME (BASOPHILISM) OF PITUITARY OR ADRENAL ORIGIN. L. R. BROSTER, Brit. M. J. **1**:425 (March 16) 1940.

Cushing's syndrome in the female is characterized by acquired hirsuties of the male type, irregularities or cessation of menstrual function and abnormal and permanent increase in weight. In the male the typical picture is one of increase in weight, diminution in the size of the external genitals and loss of sexual function. The essential difference between Cushing's syndrome and adrenal virilism is the weight factor—there is a rapid and permanent increase in Cushing's syndrome, whereas in the adrenogenital syndrome the weight usually remains stationary, or if there is an increase it is only transitory.

According to Broster, the clinical degree of virilism can be indicated by the color intensity with which the cortical cells absorb ponceau fuchsin. Patterson and Greenwood have shown an excess of androgenic substance in the urine of these patients. Marrian and Butler found pregnanetriol and isoandrosterone in the urine of patients with adrenal virilism. There have been reports of basophilism identical clinically with Cushing's syndrome which resulted from a lesion in either the pituitary or the adrenal glands. From these reports the author concludes that there must always be a hyaline change in basophilism, whereas the reaction of the adrenocortical cells to the fuchsin stain may or may not be present.

Broster describes a case of basophilism resulting from adenoma of the pituitary with a low androgen content of the urine, in which treatment with high voltage roentgen rays was unsuccessful, and a case of basophilism caused by adrenal hyperplasia with a positive reaction to the ponceau fuchsin stain and a high urinary androgen level, which was lowered by adrenalectomy. ECHOLS, New Orleans.

Treatment, Neurosurgery

RELIEF OF NEURITIS OF EIGHTH CRANIAL NERVE WITH VITAMIN B_1. K. C. BRANDENBURG, Arch. Otolaryng. **31**:189 (Jan.) 1940.

Lack of vitamin B_1 may be the basis of neuropathies regardless of the immediate cause, such as diabetes, alcoholism, pernicious anemia, poisoning with heavy metals or infectious disease. The process is one of failure of normal restoration and repair rather than of inflammation. The liver is the main storehouse of vitamin B. When this storehouse is drained by one third, the fixed supply in the nervous system is drawn on. Four fifths of the supply of vitamin B in the liver can be drained in one week when the diet is free from that substance. Most modern diets lack sufficient vitamin B. With the exception of liver and a few varieties of nuts, wheat germ and yeast, there are no foods rich in this most essential element. Loss of hearing, nystagmus and visual symptoms suggestive of retrobulbar neuropathy may be the result of lack of vitamin B. Brandenburg reports a case of severe bilateral tinnitus, of three weeks' duration, which appeared three days after a series of twenty-eight daily roentgen treatments of 303 r and one exposure to radium of 5,760 milligram hours for an epidermoid carcinoma of the cervix uteri. There were severe upper cervical and upper lumbar pain, a band-like headache above the eyes and ears and impaired hearing. Ten milligrams of thiamine hydrochloride was given intravenously for two days and increased to 15 mg. daily until the tenth day, when the tinnitus stopped. The audiometer showed improvement of hearing of 5 to 40 decibels. HUNTER, Philadelphia.

POSSIBILITY OF DIFFERENTIAL SECTION OF THE SPINOTHALAMIC TRACT. O. R. HYNDMAN and C. VAN EPPS, Arch. Surg. **38**:1036 (June) 1939.

On the basis of a careful study of the results of chordotomy in 6 cases, Hyndman and Van Epps conclude that the spinothalamic tract carrying the sensations of pain and temperature extends from a point about midway between the dentate ligament and the anterior roots to a point about midway between the anterior roots and the

anterior median fissure. The region extending 2 mm. anterior to the dentate ligament contains no fibers conducting pain or temperature. This suggests that the tract carrying such fibers lies more anteriorly than has been hitherto suspected, and hence farther away from the pyramidal tracts. Consequently, if pain can be relieved by a more anterior section less chance of involvement of the pyramidal tracts exists, and the hazard of subsequent motor weakness is materially reduced. Furthermore, these studies seem to upset the previously held concept that the fibers are arranged in a laminated fashion, those from the lowermost segments of the body occupying a place at the periphery of the tract and those from the higher segments disposing themselves toward the center of the cord. The studies indicate that fibers representing the lower segments are situated posteriorly in the tract and that fibers representing successive segments upward dispose themselves more and more anteriorly. By cutting across both anterior quadrants of the cord, pain in the chest has been eliminated without abolishing pain sensation in the lower extremities.

GRANT, Philadelphia.

GASTRIC CRISIS OF TABES DORSALIS: TREATMENT BY ANTERIOR CHORDOTOMY IN EIGHT CASES. O. R. HYNDMAN and F. J. JARVIS, Arch. Surg. **40**:286 (Feb.) 1940.

Hyndman and Jarvis are of the opinion that the reason for the lack of success in relief of the pain of gastric crisis by bilateral section of the anterolateral tracts of the spinal cord is the fact that these afferent pathways for pain and temperature have been incised at too low a level. They believe that the pain of gastric crises is probably carried in the splanchnic afferent fibers and reaches the cord over sympathetic pathways, at least as high as the third dorsal segment. On the basis of this opinion, 8 patients with severe bilateral pain from gastric crises were subjected to bilateral chordotomy at the level of the second or third thoracic segment. In all cases pain and vomiting were abolished. Retention of urine and occasional motor weakness were transient sequelae. Loss of sexual function was permanent. Considering the beneficial results of this procedure, the authors consider that its disadvantages are minimal.

GRANT, Philadelphia.

MUSCLE STRENGTH IN MYOTONIA ATROPHICA (DYSTROPHIA MYOTONICA) IMPROVED BY TESTOSTERONE PROPIONATE. F. H. HESSER, O. R. LANGWORTHY and S. A. VEST, Endocrinology **26**:241 (Feb.) 1940.

Recent studies have shown that the androgenic hormone exerts a definite influence on muscle metabolism, as expressed by the changes in the creatine-creatinine excretion ratio, as well as on the physical development of the muscle substance itself. Myotonia atrophica is a myopathy associated with gonadal atrophy, as well as with degenerative changes in the adrenal cortex. With these factors in mind, Hesser and his associates treated 2 male patients with myotonia atrophica and testicular atrophy with intramuscular injections of 25 mg. of testosterone propionate (perandren) every other day for over two months. Administration of quinine was continued. A marked improvement in muscle strength, posture and gait, and a feeling of well-being resulted as long as the drug was continued, but when it was stopped the patients returned to their original condition. A third male patient with a similar condition who was treated with testosterone propionate without quinine showed no change in the myotonia; the quinine is apparently essential for the relief of the myotonia per se, but does not improve the muscle strength. A fourth patient, a male with moderately advanced progressive muscular dystrophy but no gonadal changes, was treated with testosterone propionate, without demonstrable dynamometric response.

PALMER, Philadelphia.

ELECTRIC CONVULSION THERAPY OF SCHIZOPHRENIA. G. W. T. H. FLEMING, F. L. GOLLA and W. G. WALTER, Lancet **2**:1353 (Dec. 30) 1939.

Fleming and his associates point out that Cerletti and Bini reported in 1938 that the passage of a strong alternating current through the head usually resulted in immediate unconsciousness followed by a prolonged fit. They worked out a technic whereby this phenomenon could be used to replace the injection of convulsant drugs in the treatment of schizophrenia and administered shocks to several hundred patients. Fleming and his associates tested this method of electrical convulsion therapy on 5 schizophrenic patients. They administered seventy-five shocks, as a result of which there have been fifty major convulsions and twenty-five minor seizures. The major convulsions are similar to spontaneous ones and are followed by complete amnesia for the shock. No untoward results have been observed. The claims of Cerletti and Bini are confirmed; the method is technically effective, simple and safe and arouses no fear or hostility in the patients. No attempt is made to assess the therapeutic value of the method, which Cerletti and Bini state is the same as that of metrazol.

J. A. M. A.

EFFECT OF DEINSULINIZED PANCREATIC EXTRACT ON EPILEPTIC STATES. C. ROUVROY, J. belge de neurol. et de psychiat. **39**:676 (Oct.) 1939.

Rouvroy investigated the effect of deinsulinized pancreatic extract on the various epileptic phenomena, especially on the confusional period which follows a generalized convulsion. He studied 5 cases and was able to demonstrate reduction of the confusional period and alleviation of secondary phenomena, such as excitation, agitation, delirium and hallucinations. Hypersomnia was frequently observed, but this was less deep and less prolonged than that which occasionally follows convulsions. The extract was also demonstrated to be an active anticonvulsant in some cases in which phenobarbital failed, while in others it shortened the duration of the attacks without completely stopping them. DE JONG, Ann Arbor, Mich.

FRONTAL DECOMPRESSION FOR TREATMENT OF VISUAL DISTURBANCES ASSOCIATED WITH OXYCEPHALY. A. SCHÜLLER, Confinia neurol. **2**:303, 1939.

Roentgenograms in typical cases of oxycephaly show marked constriction of the frontal portion of the cranial capsule, and this results in incarceration of the frontal lobes of the brain and pressure on the nerves in the anterior fossa. Schüller advises decompression by the removal of the inner table of the vertical portion of the frontal bone, especially in cases in which blindness is developing.

DE JONG, Ann Arbor, Mich.

METRAZOL TREATMENT OF EPILEPSY. F. SAL Y ROSAS, Rev. de psiquiat. y criminol. **4**:709, 1939.

Sal y Rosas administered metrazol to 21 patients with epilepsy. Of these, 14 had apparently been treated systematically with phenobarbital, without relief. Most of the patients suffered from petit mal and equivalent attacks, as well as from grand mal. The procedure was begun as an experiment to distinguish between hysteria and true epilepsy; to the author's surprise, favorable therapeutic results were obtained in the group of patients with epilepsy; the present article is a systematic analysis of the data.

Many epileptic patients have convulsions after unusually small doses of metrazol, as small as 0.5 cc. The highest dose required was 6 cc. In 1 case a therapeutic remission, lasting six months, was obtained; this case was somewhat atypical in many respects. In 1 case the attacks were aggravated. In the remainder, a course of treatments (average 10.3 sessions) produced definite diminution of attacks—in 7 cases to less than 1 per cent of the original number. The interparoxysmal state

improved also in the majority of instances, notably when the disease was complicated by depressive or aggressive trends. The therapeutic effect seemed approximately as good when subconvulsive doses, producing only such symptoms as confusion, were given as when convulsive doses were used. It was better when the convulsive threshold was high than when it was low. The outlook appears more favorable for "essential" than for "symptomatic" epilepsy.

PUTNAM, New York.

WHAT IS THE EFFECT OF THE BELLADONNA ROOT ALKALOIDS OTHER THAN ATROPINE? F. DUENSING, Deutsche Ztschr. f. Nervenh. **150**:70, 1939.

Duensing made a detailed study of the pharmacologic and therapeutic effects of all the alkaloids present in belladonna root. This study was undertaken in order to evaluate the results of the Bulgarian belladonna treatment of parkinsonism. It has been stated that the wine, used in the original Bulgarian method, might increase the action of atropine by causing hyperemia of the cerebral vessels, and also by raising the temperature locally. This, however, is disproved by the fact that aqueous solutions are as effective as the alcoholic ones, or even better. The alkaloids found in the belladonna root are: hyoscyamine, atropine, apoatropine, belladonnine and scopolamine. Apoatropine and belladonnine have only recently been studied.

The result of a number of recent analyses is that hyoscyamine is the chief alkaloid of the belladonna root. It amounts to between 80 and 90 per cent of the total alkaloid content. All specimens analyzed showed in addition various amounts of atropine, between 2 and 7 per cent in one series and between 3 and 15 per cent in another. Atropine is a racemic compound of levorotatory and dextrorotatory hyoscyamine. Of these, only the levorotatory component is effective. Scopolamine is not constantly found in the belladonna root. One investigator found it in only 1 of 6 specimens tested (a little over 1 per cent); another found traces only in 2 of 11 specimens. It is therefore safe to conclude that the therapeutic result of the Bulgarian drug is not caused by scopolamine, of which only about 0.1 mg. at most would be present in a 10 mg. dose per day, while the effective dose of scopolamine is at least ten times as high. Neither could apoatropine or belladonnine be responsible for the therapeutic result of the Bulgarian drug because, as Duensing has shown, much higher amounts of these two drugs would be necessary to produce therapeutic effects.

The most interesting result of Duensing's study concerns apoatropine. This drug is closely related to atropine and can be obtained by splitting an OH group off the latter. The effects of apoatropine on the parkinsonian syndrome appear to be favorable. Duensing has given as much as from 15 to 30 mg. per day. This is in contrast to the pharmacologic experience in animal experiments, in which it was found to be very toxic. Its effects in man are essentially those of atropine, namely, loosening of rigidity and reduction, with occasional complete abolition, of tremor. In addition, however, the untoward effects caused by paralysis of the parasympathetic fibers are almost completely absent. It is administered by mouth in solution or in pills and can be combined with both atropine and scopolamine in treatment of severe conditions.

Belladonnine is a polymer of apoatropine and has little, if any, effect.

HOEFER, New York.

CONVULSION THERAPY BY MEANS OF ELECTRIC SHOCK. J. A. J. BARNHOORN, Nederl. tijdschr. v. geneesk. **84**:290 (Jan. 27) 1940.

Barnhoorn directs attention to the electric shock therapy developed by Cerletti and Bini (Sogliani, G.: New Method of Convulsion Therapy: Electric Shock Therapy, *Deutsche Ztschr. f. Nervenh.* **149**:159, 1939; abstracted, *J. A. M. A.* **113**:2100 [Dec. 2] 1939). He describes the apparatus and reports his experiences in 35 cases, in which 266 attacks were provoked. He compares the technical value

of this method with that of the metrazol shock therapy of Meduna. The therapeutic value of the method cannot be estimated as yet, but the author thinks that the electric shock therapy signifies considerable progress in the application of convulsion therapy to psychoses. The method has a number of advantages: It is easily applied, and it produces immediate loss of consciousness and complete amnesia. This is important because it eliminates the anxiety, and the patient's objection to the treatment is overcome. Moreover, the patient rapidly recovers and there are no unpleasant after-effects and secondary reactions. The method seems to be harmless.

J. A. M. A.

POTASSIUM CHLORATE IN TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS. H. J. KOLK, Nederl. tijdschr. v. geneesk. **84**:388 (Feb. 3) 1940.

Kolk directs attention to Contat's method of chemotherapy for poliomyelitis. Although this method of oral administration of potassium chlorate is still under investigation, the author thinks that the results he obtained with it justify calling attention to this procedure. The daily dose for each patient is determined on the basis of 100 mg. per kilogram of body weight. Thus, for an infant of 4 Kg. the daily dose is 0.4 Gm., whereas for a child of 20 Kg. it is 2 Gm.; the daily dose should not exceed 8 Gm. The drug is administered by mouth every two hours day and night, each individual dose constituting one twelfth of the total daily dose. If the same daily dose is given in larger fractions at less frequent intervals, there is danger of toxic effects. In addition to the oral medication the patients are given nasal instillations of 5 drops of a solution of potassium chlorate in each nostril four times a day. After two days the oral dose is reduced by omitting one daily and one nocturnal administration, and after six days the chemotherapy is stopped. The author treated some of the patients with potassium chlorate and serum and others with potassium chlorate alone. In all, the potassium chlorate therapy was used in 52 cases, and the impression was gained that the progress of the paralytic symptoms was arrested and that in the preparalytic stage paralysis was prevented.

J. A. M. A.

Diseases of Skull and Vertebrae

NEUROLOGIC PICTURE OF HERNIATIONS OF THE NUCLEUS PULPOSUS IN THE LOWER PART OF THE LUMBAR REGION. R. GLEN SPURLING and EVERETT G. GRANTHAM, Arch. Surg. **40**:375 (March) 1940.

Spurling and Grantham stress the high percentage of cases in which the diagnosis of rupture of an intervertebral disk can be made without the use of contrast myelography with either oil or air. Their series includes 125 consecutive laminectomies performed for intractable pain low in the back and for sciatic pain. In 92 of these cases frank rupture of the annulus fibrosus with herniation of the nucleus pulposus was revealed. In 18 cases there was hypertrophy of the ligamentum flavum, in 4 a neoplasm in the lower lumbar portion of the canal, and in 11 no abnormalities on exploration were observed. The incidence of ruptured intervertebral disk at the fourth and fifth lumbar interspaces was 99 per cent. Twenty-seven patients were operated on on the basis of the clinical signs alone.

In summarizing the signs and symptoms, the following localizing data are tabulated: *Third Lumbar Interspace.*—(1) disability of the lower part of the back, with local tenderness at the third lumbar spine and reduction of lumbar lordosis; (2) presence of Lasègue's sign; (3) positive Naffziger test, producing paresthesias in the fourth and fifth lumbar dermatomes; (4) reduction or absence of the knee jerk, the ankle jerk being unchanged, and (5) hypesthesia and paresthesias in the fourth and fifth lumbar dermatomes.

Fourth Lumbar Interspace.—(1) disability of the lower part of the back with stiffness of the lumbar portion of the spine and localized tenderness at the level

of the fourth lamina, with reduction of lumbar lordosis; (2) Lasègue's sign; (3) positive Naffziger test, with paresthesias involving the fifth lumbar, the first sacral and perhaps the second sacral dermatome; (4) no involvement of the ankle and knee jerks, and (5) hypesthesia and paresthesias in the fifth lumbar and first sacral dermatomes.

Fifth Lumbar Interspace.—(1) disability of the lower part of the back, with absence of lumbar lordosis and localized tenderness to pressure over the fifth lumbar vertebra; (2) Lasègue's sign; (3) positive Naffziger test, producing paresthesias radiating into the first and second sacral dermatomes; (4) diminution or absence of ankle jerk, and (5) hypesthesia involving the first and second sacral dermatomes.

That these neurologic symptoms and signs are accurate and reliable is attested by the fact that during the past eight months 26 consecutive herniations of the nucleus pulposus have successfully been removed, without confirmation with iodized oil or other contrast mediums. In the twenty-seventh case, confirmation of the clinical findings was not made at operation. In the same period iodized oil has been used in 28 cases for verification of the lesion. In 12 cases in this group the clinical findings were sufficiently clearcut to justify surgical exploration without iodized oil, but for various reasons roentgen verification was demanded. In the group in which iodized oil was used there were 4 failures of verification. In 2 cases of this group the clinical picture definitely pointed to herniation at the fifth lumbar interspace, yet the iodized oil study indicated the lesion to be at the fourth lumbar interspace. The accuracy of the clinical findings in both instances was confirmed, whereas the defects observed with iodized oil were explained only by the presence of a hypertrophied ligamentum flavum. On the basis of their experience thus far, the authors feel much safer in subjecting patients to operation when the clinical findings are clearcut than when an iodized oil study is necessary for accurate diagnosis.

GRANT, Philadelphia.

PATHOLOGY OF THE INTERVERTEBRAL DISK. JOHN B. DEC. M. SAUNDERS and VERNE T. INMAN, Arch. Surg. **40**:389 (March) 1940.

The intervertebral disks make up a full quarter of the total length of the presacral portion of the spinal column and therefore constitute an extensive organ. The essential unit is made up of three parts: the annulus fibrosus, the nucleus pulposus and the cartilage plates. The cartilage plates cover the end surfaces of the opposed vertebral bodies. Grossly, they are well defined centrally, but they disappear marginally by blending with the annulus fibrosus. Microscopically, the plate is composed predominantly of hyaline cartilage, which is fibrous at the periphery.

The nucleus pulposus occupies approximately the center of the disk, a little nearer the posterior than the anterior aspect. The nucleus is soft and elastic, somewhat slimy to the touch, and because of its inherent turgor, bulges on section above the cut surface. Histologically, the nucleus consists of a loose network of delicate fibrous strands with a variable number of cellular elements enmeshed. Centrally, the arrangement tends to be highly irregular, or the ground substance may be more homogeneous and relatively structureless. Aggregations of notochordal tissue are more definite in this region.

The annulus is composed of heavy collagenous bands, which become coarser as the margins of the disk are approached. The innermost fibers pass into the peripheral edges of the cartilage plate. Those intermediate in position gain attachment to the bone as the fibers of Sharpey, while the most external bundles blend with the adjacent ligaments and fibrous periosteum of the centrum.

The intervertebral disk plays a most important part in the functional mechanism of the spinal column. Not only does it permit movement to occur between the series of vertebral segments but it is related to the transmission of body weight, to the absorption and dispersal of the multitudinous shocks to which the column is constantly exposed and to the maintenance of the spinal curves. The

elastic turgor of the disk exerts an expansile force on the opposed vertebral bodies, which is resisted by the various spinal ligaments, thereby establishing a state of internal equilibrium that serves both to resist deforming forces and, when deformity has occurred, to restore the column to its normal position.

It has been demonstrated that the axis of movement between adjacent vertebrae over a limited range passes through the nucleus pulposus. The substance of the disk is such that any absolute change in its size is exceedingly small. Movement occurs by change in shape. In flexion there is compression of the disk anteriorly and expansion posteriorly, and during extension, anterior elongation and posterior compression. Should extension continue to the point at which the spinous processes contact one another, this point of contact becomes the fulcrum and further extension leads to elongation of the entire disk with narrowing of its diameter. This alternating compression and extension of the disk produces displacement of the nucleus pulposus, posteriorly in flexion and anteriorly in extension. Lateral flexion displaces the nucleus slightly to the contralateral side.

These movements, particularly those of a shearing nature, not only are expressed in the morphologic appearance of the disks at various levels, but are of considerable significance in the production of the various types of anterior and posterior fissuring of the annulus, in the pathologic displacements of the nucleus and in the deformities of the spine, such as scoliosis, which attend degeneration of the disk.

Throughout life the intervertebral disks are subject to continuous and progressive changes of structure of a character so marked as to make it difficult to determine what is normal and what is pathologic. Degenerative phenomena are so frequent in supposedly healthy spinal columns at middle age that the changes must be regarded for the most part as the outcome of age processes in an organ subjected to destructive forces of considerable magnitude as represented by functional activity. The commonest morbid changes would seem to be related to desiccation occurring prematurely or to an excessive degree. The cartilage plates, enclosing the nucleus, would seem to constitute the part of the disk most resistant to degenerative phenomena. They are, however, of the greatest importance, in that solution in their continuity allows escape of nuclear material, with consequent loss in elasticity and degeneration of the disk as a whole. The changes in the cartilage plates may be primary or secondary to degeneration of the disk or to disease within the bony vertebral body.

Traumatic rupture of the cartilage plate occurs in conjunction with compression fracture of the vertebral body, but it has been remarked how often the disk escapes injury even in the most severe lesions. Rupture of the cartilage plate occurs secondary to loss of support of the spongiosa of the vertebral body. The commonest form is that associated with senile osteoporosis of the spine. Similar rupture of the cartilage plate follows loss of bony support due to invasion of the vertebral body by infection or tumor. The nucleus pulposus varies considerably in structure from infancy to old age. In infancy the nucleus is well defined, and its line of demarcation from the annulus is distinct. Degeneration may occur as early as the third decade or before if the integrity of the disk has been interfered with by trauma or congenital defects in the restraining cartilage plates. The annulus fibrosus likewise shows progressive changes during its life history. With increasing age the fibrous lamellae become progressively more definite and larger. With the onset of degeneration the inner layers merge into the expanding nucleus until little more than a ring of the original tissue persists.

From the pathologic point of view, posterior displacements of the disk tissue are formed with the greatest frequency in the spinal columns of elderly persons. They are found most frequently in the lower thoracic and lumbar regions and are nearly always attended by definite evidence of disk degeneration. The thoracic protrusions tend to be small and insignificant, often buried beneath the posterior longitudinal ligament. In the lumbar and cervical regions they are larger and frequently extend to one or the other side of the midline. Histologically, the material obtained post mortem or at operation presents an extremely variable picture. In some specimens the structure is characteristically that of the nucleus

pulposus, although as a rule the cellular elements are increased and there is true inflammatory reaction. In others, and perhaps the great majority, there is a mixture of pulposal and annular material showing a varying degree of cartilaginous metaplasia, inflammatory reaction or necrosis. Some discussion has arisen as to whether these nodules are herniations of nuclei or protrusions of intervertebral disks. In the opinion of the authors both varieties may be found. In some cases they have seen fissuring of the annulus surrounded by "brown degeneration" with herniation of nuclear material. In others they have found collapse of the disk and protrusion of the annulus with or without herniation of the nucleus. These findings are nearly always attended by profound degeneration of the disk. With respect to younger subjects with otherwise healthy disks, the question arises as to whether trauma is not the main causal agent. The authors doubt whether in such subjects trauma would rupture the annulus; it would be more likely to fissure the cartilage plate at the junction with the annulus, and the finding of a portion of the plate in the extruded material is suggestive of this mechanism. The authors emphasize that posterior herniations are in the great majority of instances evidence of general disk degeneration.

GRANT, Philadelphia.

IODIZED OIL MYELOGRAPHY: USE IN THE DIAGNOSIS OF RUPTURE OF THE INTERVERTEBRAL DISK INTO THE SPINAL CANAL. AUBREY O. HAMPTON, Arch. Surg. **40**:444 (March) 1940.

A positive diagnosis of posterior protrusion of an intervertebral disk into the spinal canal has been made in 133 cases by the use of iodized oil, roentgenoscopy and instantaneous films taken during roentgenoscopic examination. All except 9 of these diagnoses were proved correct at operation. There were 2 cases of negative results on roentgen examination with positive operative findings and 2 of questionable roentgen diagnosis with positive operative findings. A dilated arachnoid vein, a fractured pedicle, a small osteoma and, in 2 cases, a thickened ligamentum flavum were misinterpreted as ruptured intervertebral disks. Surgical exploration has been done with negative results in 9 cases, of which negative results were expected from roentgen examination in 7 and positive results in 2. The accuracy of diagnosis is therefore 93 per cent. Air myelography is rapidly coming into use in the diagnosis of rupture of the intervertebral disk. The accuracy of this type of examination varies considerably in the hands of different workers. At present it is doubtful whether a positive diagnosis of rupture of an intervertebral disk can be made in over 50 per cent of the cases. Even if an error of 50 per cent in the diagnosis of rupture of the disk by air myelography persists, the procedure should nevertheless be used as a preliminary to the injection of iodized oil, because in that way it will probably be possible to eliminate the use of iodized oil and its questionable ill effects in one-half the cases. Air myelography is of distinct value when the findings are unequivocally positive, but it is of little value when the findings are equivocal or negative.

GRANT, Philadelphia.

INTRASPINAL PROTRUSION OF INTERVERTEBRAL DISKS. J. GRAFTON LOVE and MAURICE N. WALSH, Arch. Surg. **40**:455 (March) 1940.

In an analysis of 500 consecutive cases in which operation was performed for protrusion of one or more intervertebral disks, 58 per cent of the patients gave a history of a specific injury to the back. Many patients when they give their history for the first time fail to mention any past injury; however, when more closely questioned regarding accidents and injuries many of them recall some episode followed by backache which subsided after a reasonable length of time. Many of these persons had not connected their presenting chief complaint of backache or sciatic pain with the injury. This is true particularly if there has been a long interim of freedom from pain. Eighty-four per cent of the 500 patients had intermittent symptoms.

Protrusion of any intervertebral disk may occur, but in the vast majority of cases the protrusion occurs in the lumbar region of the spinal canal. Approximately

96 per cent of 500 patients had lumbar protrusion. In this series there were 358 men and only 142 women who were operated on because of protruded disks. This cannot be taken to indicate that the male back is weaker. It means probably that the discrepancy is due to the etiologic factor, trauma, which has a greater chance to exert itself among men, who ordinarily do most of the heavy lifting and straining, and who, in industry, are more likely to be injured. The average age of the patients at the time of operation was 40 years. It should be noted that most of the patients had had intermittent symptoms for several years before the true cause of the disability was discovered; hence the protrusion occurred probably at an earlier age.

The most common and valuable symptoms and signs were unilateral sciatic pain, which occurred in 78 per cent of patients, and bilateral sciatic pain, which was present in 16 per cent. In the other 6 per cent, backache alone or extension of pain elsewhere than along the course of the sciatic nerve occurred. Twenty-four per cent of the patients complained of pain which interfered with sleep at night. This is an important symptom when present. It is particularly suggestive of a lesion of a nerve root, but it is much more common in cases of intraspinal neoplasm than in those of protruded disk. Another indication of involvement of a nerve root or of radicular type of pain is accentuation of the pain on coughing, sneezing or straining at stool. Such accentuation occurred in 64 per cent of the cases. Paresthesias in the dermatome supplied by the compressed nerve root are of value in the diagnosis and localization of the protrusion. Paresthesias occurred in 50 per cent of the cases. On the other hand, sphincteric disturbance occurred in only 4 per cent.

The three neurologic signs which continue to be the most helpful in the diagnosis of protrusion of a lumbar disk are Lasègue's sign (84 per cent), sciatic tenderness (64 per cent) and diminution or absence of the achilles reflex on the side of the pain (60 per cent).

In only 25 per cent of cases was there any muscular weakness; sensory loss was detected in only 21 per cent. This is not difficult to understand in the light of the fact that the protrusion usually is small and compresses only one nerve root. Examination gave objectively negative results neurologically in 20 per cent of cases, except for a positive Lasègue's sign or sciatic tenderness or both. All patients suspected of having a protruded intervertebral disk should undergo a diagnostic lumbar puncture, so that the hydrodynamics of the spinal fluid may be studied and a specimen of the fluid obtained for careful analysis. As has been stated, a protruded disk rarely produces subarachnoid block, particularly a disk in the lumbar region of the spinal column. The detection of such a block, therefore, would be suggestive of the greater likelihood of an intraspinal neoplasm. The most important finding in the analysis of the spinal fluid in such cases is the total protein content of the spinal fluid. In the entire series, 40 per cent of the patients had less than 40 mg. of total protein per hundred cubic centimeters of spinal fluid in the specimen submitted for analysis.

The accuracy of the detection or the exclusion of intraspinal lesions by means of iodized poppy seed oil was high, greater than 90 per cent. Because of the fact that radiopaque oil is absorbed slowly from the subarachnoid space, it should not be used in questionable cases, especially if the patients are not to have an operation.

GRANT, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND SECTION OF NEUROLOGY AND PSYCHIATRY, NEW YORK ACADEMY OF MEDICINE

E. D. FRIEDMAN, M.D., *President of the New York Neurological Society, Presiding*

Joint Meeting, May 7, 1940

Periodic Dulness as an Epileptic Equivalent. DR. TRACY J. PUTNAM, DR. H. HOUSTON MERRITT, Boston (by invitation) and DR. JERRY PRICE, Boston (by invitation).

"Epileptic deterioration" is a phenomenon which has long been recognized. It is usually ascribed to degenerative changes in the brain, and there can be no doubt that these occur in many cases as a result either of an organic disease primary to the attacks or of the attacks themselves. The convulsive state brings other dangers to the patient's mentality. A third cause of degeneration is the excessive use of sedative drugs. A fourth is the psychologic burden of being subject to a disorder which is potentially disastrous to economic and social life and carries with it a constant threat of humiliation.

There appears to be a fifth type of intellectual disturbance in many cases of epilepsy, which has received little attention. It is a temporary dulling of intellect, often described by the patient as being "like a mist," which may last for hours or days. It often occurs just before or after manifest seizures, but sometimes independently. During such periods the patient appears reasonably well, goes about his occupations and is only vaguely conscious that something is wrong. He is, however, usually unable to follow a complicated story, to do more than the simplest mathematical problems or to plan constructive work. Affective phenomena, such as irritability, ordinarily regarded as the essential feature of psychomotor attacks, are usually absent. Eight cases are reported to illustrate the condition, which is common.

It is suggested that the temporary dulness is the result of a disordered function of the brain, such as presumably occurs in "subclinical" attacks, as revealed in the electroencephalogram. The reasons for this belief are three: First, the condition is usually recognized by the patient as temporary, and he is often well and alert between such episodes; second, subclinical attacks are often accompanied by prolongation of the reaction time, and electroencephalographic studies on the patients in this series have usually shown abnormalities, in some instances more pronounced during the period of dulness; third, improvement in intellectual performance has occasionally been reported to follow medication with phenobarbital, and was usually produced in the patients in the present series by the use of dilantin sodium and other therapeutic measures, such as exercise.

DISCUSSION

DR. RICHARD BRICKNER: Are all the episodes of dulness periodic, or are they sometimes continuous and chronic? Perhaps they are both. Certainly some are periodic, and I shall discuss these. First, it is to be noted that periodic dulness can reach a point at which thought becomes completely fixed, or even abolished for the moment. This is a well known phenomenon in oculogyric crises; there are patients who begin the crises with a sudden blanketing, in which either a thought which is present becomes fixed or no thought process is possible at all.

I suggest that this is akin to what Dr. Putnam has described. There are other manifestations of the same process which occur in cases of epilepsy—abrupt changes in thought. Sometimes one observes a sudden termination of all thinking. One can also observe the reverse, as I did in an elderly man with arteriosclerosis, who did not have epilepsy as such, with seizures, but suffered from a condition which Dr. Putnam includes under the nonseizure type. The case occurred before electroencephalographic examination was possible. The patient had attacks which clinically were periodic spells of a condition just the reverse of periodic dulness, namely, streams of thought. He would become possessed by an uncontrollable stream of thought, chiefly about death, always about something unhappy, which would come suddenly and terminate just as suddenly. Dr. Davidoff has observed such a case, which he described, and previous to that 2 others. One of the early cases was that of a little girl whose sole symptom of an oligodendroglioma of the parietal lobe was the periodic sudden utterance, with subsequent amnesia, of "Pooh-pooh to the Devil, and a kiss to God." My associates and I have also studied a girl with a verified spongioblastoma of the temporal lobe whose seizures, of which there were many, were initiated by an abrupt requirement to think a certain thought. All of these manifestations may represent the counterpart of what Dr. Putnam describes. We also studied a patient at the Neurological Institute two years ago who suffered from fixation of both gaze and thought. This was perhaps another matter, but again it showed how the process of epilepsy can act on the neurons of intellect. This patient would have sudden fixation of gaze, so that one could not make him look at anything else, and coincidentally and similarly fixation of attention, so that his thought could not be diverted from what it was on.

Foerster made a remarkable observation during an operation on a tumor of the third ventricle; when a tampon was placed on one part of the wall the patient began a flow of language which sounded to Foerster like manic speech. There were clang associations, overproductivity and obscenity. As soon as the tampon was lifted the stream of language ceased. This performance could be repeated at will; subsequently, 4 or 5 other patients were made to behave in the same way. I give these illustrations to show that neurons of thought, as such, can be affected by physical processes just as can those of motor, sensory or other activity.

In addition, thought, or what appears to be a manifestation of thought, can be equally influenced by electrical stimulation; I have seen this brought about at least once. In this instance the stimulus was furnished by an electrode instead of a tampon. Dr. Masson last year explored the cortex of an epileptic woman under local anesthesia in seeking for an epileptogenous zone. None was discovered, but when the stimulus was applied to a certain area on the mesial side of the left cortex the patient was obliged to repeat whatever letter she was naming at the moment, during a recital of the alphabet.

Dr. Putnam suggests that some patients who do not appear clinically to be epileptic, according to present orthodoxies, but who, nevertheless, suffer from periodic phenomena of one kind or another may be discovered to be epileptic and deserve to be treated as such. In my opinion, the suggestion is a fine one and should be accepted. I think the phenomenon Dr. Putnam has talked of should be regarded in this way, so that the truth can be tested. The same may be said for the endless variety of other phenomena in which sudden periodic alterations of intellect and emotion occur.

The Place of Electroencephalography in Clinical Neurology: A Retrospective and Prospective Study. HERBERT JASPER, D. ÈS SC., Montreal, Canada (by invitation).

It has been about ten years since Hans Berger published his demonstration that the electrical activity of the human brain can be recorded through the unopened skull. It has been about five years since Adrian and Matthews convinced the scientific world that Berger's work was sound, thus opening the floodgates for a general inundation of brain waves from all quarters. In a remarkably

short time the human brain in almost every normal and pathologic condition has been made to trace its varied waves on miles of running paper. Great hopes have been expressed for the application of this new technic to many of the knotty problems of neurology and psychiatry. What are the established results to date, and what is the prospect for the future?

Standardization.—A fair degree of standardization has been achieved with regard to general forms of recording apparatus and technic except for certain details, some of which may be important. A set of standard electrode placements has been developed at the Montreal Neurological Institute providing for numerical designation of measured points covering the entire surface of the scalp. This has been adopted by a few other laboratories. Most individual laboratories have their own, often haphazard, system of scalp positions. A general agreement among electroencephalographers might serve to facilitate reproduction of results.

The principal varieties of waves and patterns have all been described, and general agreement has been achieved with regard to some of the basic terminology. Alpha and some beta waves have been accepted as the most prominent feature of the normal electroencephalogram. All waves between 1 and 6 per second and random slow waves, that is, those below the normal alpha range, are called delta waves, in accordance with the suggestion of Walter for the slow waves recorded from the vicinity of an expanding lesion. Since slow waves arise from a great variety of causes, all related to depression of cortical function, as in normal sleep, there may be some justification for use of the single term to cover such a wide variety of pathologic and even normal conditions. More specific terms will probably arise as more is known regarding the fundamental basis of delta activity. Some delta activity is seen in the electroencephalogram of the normal person when awake, and some apparently normal persons show a fair amount. This provides a troublesome border zone which is in need of clarification. General agreement as to the interpretation of such records has not been reached.

The Epilepsies.—Two general classes of abnormalities are recognized in the electroencephalogram: abnormal rhythms, which Lennox has termed the "dysrhythmias," and abnormal amplitudes, which my colleagues and I have called the "hypersynchronies." In general, the slow dysrhythmias are caused by a variety of conditions which depress or inhibit cortical function, while the rapid dysrhythmias are related to increased excitatory states of the cortex; the normal is represented by a balance between the two extremes. The hypersynchronies are found only in cases of the epilepsies or allied epileptoid conditions. Hypersynchronies are usually associated with some form of dysrhythmia, but may occur without abnormal rhythms, as when there is a sudden increase in amplitude of 10 per second (alpha?) waves. Epilepsy is better described as a "paroxysmal hypersynchrony" than as a "paroxysmal dysrhythmia."

The electroencephalogram has become a valuable guide in the handling of epileptic patients. The preliminary classification of the epilepsies as grand mal, petit mal and psychomotor attacks on the basis of electroencephalographic patterns has not been found satisfactory in the hands of most investigators, owing principally to the lack of close correspondence between clinical observations and the electroencephalographic patterns. At the Montreal Institute we have concluded from our studies that the form of the clinical attack, as well as the form and localization of the electroencephalographic patterns, is more clearly related to the localization of cerebral areas and the principal neuronal circuits involved than to any fundamentally different mechanisms of epileptic discharge.

Direct recording from local epileptogenic lesions shows a specific form of electrical discharge closely related to the "strychnine spikes" familiar to animal experimenters.

Localization of Cerebral Lesions.—Restricted cerebral lesions can be localized with reasonable accuracy by the electroencephalogram in 90 to 95 per cent of verified cases. Extensive experience and sagacity of interpretation are necessary for this degree of success to be realized, owing to the complicated, and often

poorly understood, electrophysiologic principles involved. The electroencephalogram does not, and probably will not, replace the pneumoencephalogram, except in particularly cleancut cases in which the pneumoencephalogram is inadvisable and corroborative clinical evidence is available.

Acute Injuries to the Head.—The electroencephalogram is particularly sensitive to cerebral damage due to injury to the head. It has proved of great value in estimating the degree and localization of injury and in following improvement, as well as in distinguishing neurosis, malingering and actual "organic" residuals of cerebral trauma.

The Psychoses.—A wide variety of abnormalities and many normal records are found among psychotic patients. This serves to emphasize again the symptomatic character of most psychoses. Little order has yet appeared from the attempt to apply this new technic to psychiatric problems, except for the discovery of many hitherto unsuspected localized cerebral lesions which form the basis for psychotic behavior. Further progress, but no revolutionary achievement, may be expected in this complicated field.

Heredity.—A strong hereditary factor in determining the form of the electroencephalogram has been established. The importance of this finding as related to investigations of the heredity of cerebral disorders, especially the epilepsies, can hardly be overestimated. Results are too recent and too few at present, however, for proper evaluation of this work.

Conclusion.—It can be stated that the electroencephalogram has come to stay as a valuable diagnostic aid in neuropsychiatric practice. One might say that in the proper handling of the epilepsies it is almost indispensable, that in the localization of cerebral lesions it offers a definite advantage and that in the examination of injuries to the head it is of value in cases in which the diagnosis is questionable. In other disorders it is still only a research tool, with some promise. Future progress in this new field depends more on the development of satisfactory interpretative principles than on the recording of more and more brain waves.

DISCUSSION

Dr. Leo M. Davidoff: It is a privilege to hear this illuminating presentation by Dr. Jasper. Dr. Jasper, I believe, was the author of the first paper on electroencephalography in the United States, and has been in the vanguard of research in this field since. At the Jewish Hospital in Brooklyn we owe a particular debt of gratitude to him, because his pupil, Dr. Margeret Rheinberger, is in charge of the department and most of the work of this nature has been done by her.

With respect to a few of the points which Dr. Jasper mentioned: I wish to cite a case illustrating the reversibility of these abnormal electrical waves. A Negro girl presented signs of a tumor of the left frontal region, with positive Wassermann reactions of the blood and spinal fluid, and my colleagues and I concluded that the lesion was a gumma. Displacement of the ventricular system to the right was revealed by a pneumoencephalogram. Antisyphilitic therapy was administered, without operation, except right subtemporal decompression to relieve papilledema, and in a few months there was complete reversal of the electrical activities; a second pneumoencephalogram showed return of the ventricles to the normal position.

With regard to another point: I wish to put myself on record as going a step beyond the position which Dr. Jasper has indicated is Dr. Penfield's. While one likes, if possible, to make a diagnosis and localization of tumor of the brain, I have operated in the past, as I shall occasionally do in the future, on patients who show clinical evidence of a localized lesion and confirmatory evidence of this localization in the electroencephalogram and for whom pneumoencephalographic examination, either by the lumbar route or directly by injection into the ventricles, would be a dangerous procedure. In cases of this sort I am willing to operate without pneumoencephalographic verification. This is simply a step forward to

the attitude which obtained before the electroencephalographic test was available, when one would operate on patients with cerebral tumor on clinical evidence alone.

Dr. Jasper has indicated that this form of investigation is occasionally productive of headaches for the investigators; I shall not go into this negative phase, which he has illustrated. Perhaps I can better confirm what he has said by a brief summary of our experience with this method. I shall divide the cases in our experience into three groups, and summarize them briefly.

The first is a group of 81 cases in which eventually, at the time of discharge of the patients, the diagnoses of suspected tumor, cortical atrophy, porencephaly, cerebral vascular disease, psychoneurosis and the like were made. In 36 of these 81 cases, we obtained a characteristic localizing abnormality in the pneumoencephalogram. In 45 the pneumoencephalograms were normal. In only 15 did the electroencephalogram show characteristic localizing signs; in 31 they displayed definite diffuse abnormalities, indicating diffuse organic disease of the brain; in 14 slight abnormalities and in only 21 essentially normal tracings.

In another group of 68 cases the primary reason for entrance to the hospital was convulsions. In 26 instances the condition proved on pneumoencephalographic examination or at operation to be tumor of the brain. In 25 of these 26 cases there were definite localizing electrical abnormalities that corresponded exactly to the localization of the tumor by one or the other of the confirmatory methods. In only 1 were the electrical tracings normal. In 16 cases of the group atrophy of the brain was shown in the pneumoencephalogram; in 13 localizing abnormalities appeared in the electroencephalogram, and in 3 there were no abnormalities. In 26 cases the pneumoencephalogram appeared normal; in only 4 of these 26 cases was the electroencephalogram normal. In 18 of the 26 cases there were diffuse abnormalities, some of them including epileptic discharges.

In the group of 107 cases of cerebral tumor there were 71 tumors of the hemispheres, such as meningiomas and metastatic tumors. Definite localization was shown in the electroencephalogram in 65 cases and fair localization in 3, by which I mean that the localization did not correspond exactly to that observed at operation, and the electroencephalogram was essentially normal in 2. In 1 case the electrical tracing was diffusely abnormal, such as Dr. Jasper has described in association with marked increase in intracranial pressure. Of the 16 cases of tumor of the posterior fossa, suggestive localization was indicated in 9, diffuse abnormalities were shown in 3 and normal conditions in 4. Tumors, such as tumors of the pituitary gland and suprasellar meningiomas, were located in the region of the chiasm in 10 cases. In only 1 of these, a case of meningioma which extended to the middle fossa on the left side, was there definite localization. We did not make use of the pharyngeal lead which Dr. Jasper has described; perhaps by so doing one could obtain more localizing changes in cases of this type. In 2 cases of tumor of the third ventricle only diffuse abnormalities were shown, without localization. Of 5 cases of subdural hematoma, there were definite localizing changes in 1, diffuse abnormalities in 2 and tracings within normal limits in 2.

In 2 of 3 cases of abscess of the brain the electroencephalographic changes were localizing.

Thus, of the total of 107 cases of tumor of the brain, we had 69 (including cases of chiasmal lesions and the like) in which there was definite localization, 3 in which there was fair localization, 10 in which there were suggestive localizing changes, 9 in which there were diffuse abnormalities and 16 in which the pattern was normal.

We believe, as Dr. Jasper has stated, that the electroencephalographic method has come to stay, and that it is of the greatest value as an additional aid in the localization of tumors and other focal abnormalities of the brain. It is of great value in making the differential diagnosis of organic and functional disease of the brain, but it is a means of examination which cannot stand alone, without support from other methods.

DR. HERBERT JASPER, Montreal, Canada: Dr. Davidoff's findings, I think, are similar to ours, and the results of the work he has been doing are surprisingly good. I wish to thank him for his interesting discussion.

I am sure that Dr. Putnam has ideas concerning epilepsy that may not coincide exactly with those I am expressing. I am sorry that time does not permit his discussion. The idea that all forms of epilepsy are focal, but in different parts of the brain, is a working hypothesis similar to that proposed originally by Hughlings Jackson. I do not mean to disregard biochemical precipitating factors that are known to elicit convulsions without an apparent focal onset.

The Repetitive Core of the Neurosis. DR. LAWRENCE S. KUBIE.

The nuclear problem in the neurosis is presented by the repetitiveness of its phenomena. No interpretation of the neurosis that fails to account for this crucial point is adequate. An effort to explain this phenomenon is presented in the following terms: 1. All psychologic phenomena are and must be, by their very nature, repetitive. The reasons for this fact are developed in detail in the paper.

2. All neurotic psychologic phenomena are dependent on a distortion of this normal and inevitable repetitiveness of all psychologic phenomena. The forces which are at work to produce this distortion of normal repetitiveness are discussed in detail.

3. All neuroses, therefore, no matter with what specific symptoms they may present themselves, are found on careful and critical examination to consist of certain obligatory repetitions. These obligatory repetitions depend on the distorted repetitive mechanism, and for special reasons single out now one and now another manifestation for repetitive emphasis.

4. The so-called obsessional or compulsion neurosis, and the perversions as well, are merely special forms of this neurotic distortion of normal repetition.

5. One may, therefore, have to revise analytic conceptions of the dynamic mechanisms which are specific for the obsessional symptomatology and for the obsessional character, since these would seem to be only special manifestations of a general process.

Various possible explanations of the distorted obligatory repetitiveness of the neuroses, including possible organic factors, are considered. The thesis is presented, however that the obligatory repetition becomes the only final common path of expression for multiple pairs of opposing feelings and opposing impulses. Every repeated neurotic symptom is seen to express several pairs of irreconcilable opposites—a demand and its surrender, anger and fear, defiance and submission, self vindication and guilt. That is why the analytic explanation of any symptom, such as a dream, must always depend on pairs of opposing reasons, which are apparently inconsistent and paradoxic. This is also why the repetition of the symptom becomes uncontrollable, because in fact there is never an adequate cause for stopping. If the same symptom expresses both defiance and submission, when the patient for a moment gives up his defiance the symptom appears to express his submission; when he momentarily stops his submissiveness, the symptom appears to express his defiance.

The ontogenic development, or the evolution, of the neurotic process is outlined, with an explanation why the first neurotic manifestation must always be a compulsive act, to be followed by obsessional thoughts and then by the breaking through of anxiety and other disturbances in mood. To this are added the influence of fantasy and an explanation of why the acquisition of the power of fantasy inevitably increases both normal and pathologic repetitive phenomena.

Finally, the relation of the focus of the obligatory repetitive process to the choice of neurosis is discussed. It is shown that the repetitive process can be focused on instinctual acts themselves, giving rise to perversions; on secondary reactions, giving rise to the various congeries of psychoneurotic symptoms, or on the emotional reactions to the conflict, giving rise to states of fear, anxiety, rage

and depression. The total neurosis is pictured, therefore, as consisting of three basic components: (1) a constellation of more or less obligatory and compulsive libidinal activities; (2) a constellation of various forms of indirect "psychoneurotic" representatives of or reactions against these activities, and (3) a constellation of emotional reactions. In certain neurotic pictures the libidinal activities receive the major emphasis, giving rise to what are commonly called the perversions. In others the secondary reactions receive major emphasis, giving rise to what are ordinarily called the psychoneuroses. In a third type the emotional reactions are given major emphasis, giving rise to what are ordinarily called the anxiety states and the emotional disturbances. However, no matter which third of the total picture receives predominant emphasis, when one penetrates below the surface one always finds at the core an underlying compulsive obsessional situation. That is why all neuroses on analysis turn out to be "mixed neuroses."

The relation of this formulation to the classic etiologic picture of the neurosis is described, as well as its relationship to traumatic life incidents. Finally, a tabular outline is presented as the basis for a new classification of the neuroses.

Manifested Continuously	Manifested Intermittently or Alternately	Masked Continuously	Subgroup
Group 1			
Frank moods Anxiety Anger Depression Elation	Perversions	Psychoneurotic symptoms	A
	Psychoneurotic symptoms	Perversions	B
Group 2			
The various constellations of psychoneurotic symptoms	Perversions	Moods	A
	Moods	Perversions	B
Group 3			
Perversions	Moods	Psychoneurotic symptoms	A
	Psychoneurotic symptoms	Moods	B

DISCUSSION

DR. BERTRAM D. LEWIN: I have had the privilege of reading this paper in several drafts. I find it essentially a closely reasoned analysis of great significance, an *Ernstmachen,* as the Germans put it, with the principle of repetition applied more consistently than in any paper that has appeared since Freud introduced the idea of a repetition compulsion. Freud introduced the term "repetition compulsion" to refer to well known factual matters: the repetitive dreams, the traumatic neurosis, the transference situation and certain types of play in children, in which, aside from the pleasure principle, he saw a phenomenon of the repetition compulsion in pure culture. Essentially Dr. Kubie does not differ from Freud, as he has made clear in his summary. He takes the repetition principle seriously, works out its role in nosogenesis carefully and plausibly and traces it through Freud's old theory of the structure of a neurosis: internal conflict, external conflict, frustration and symptom formation. Whereas Freud found for the repetition compulsion a biologic substratum in the work of Weismann and in that of Woodruff on Paramecium, Dr. Kubie has found neurologic correlates for this compulsion. He is certainly and acceptably bringing the subject into a field where there may be experimental demonstration. He indicated as much when he criticized the Russian work on the experimental production of neurosis merely from the standpoint that it had not been sufficient. I wish again to express my appreciation of Dr. Kubie's interesting paper.

Book Reviews

Tratado de enfermedades nerviosas. By Luis Barraguer Ferre, Ignacio de Gispert Curz and Emilio Castaner Vendrell. Price not given. Vol. 1, 1936, pp. 1,154. Vol. 2, 1940, pp. 1,108. Barcelona: Salvat Editores, S. A.

This is a remarkable textbook of nervous diseases in two large volumes, which represents an extensive survey of the literature with many observations which are obviously original. It is written in a clear, somewhat didactic style, is easy to read and is beautifully illustrated with numerous original photographs and some instructive diagrams. The text as a whole is larger than the last edition of Oppenheim or Wilson's posthumous textbook, but this is chiefly because the print is unusually large and readable. In general, the treatment of the subject matter follows the custom of French and English textbooks in giving a single point of view about most subjects, rather than in approaching the completeness of Oppenheim's book. The first volume was published in 1936; its contents seem already a little old, although the important fundamentals are there and well expressed. There is a graceful, brief introduction by Pierre Marie, reproduced in his own handwriting.

The book begins with a long section on examination of the nervous system, which is, in general, graphically described for the practitioner or student. In the discussion on examination of the ear no mention is made, however, of the audiometer, now so generally useful in the United States. The determination of spinal fluid pressure and the significance of cytologic and chemical changes in the fluid are rather slurred over. As one would expect, electroencephalography is not mentioned at all in the first volume and only briefly in the second. There is a long, enthusiastic section on electrodiagnosis, which appears to accept the classic point of view rather uncritically.

The section on diseases of the peripheral nerves is particularly noteworthy for its chapter on the problem of leprosy, which is profusely illustrated. There is no mention of the possible role of dietary deficiency in the polyneuritis of alcoholism, diabetes and pregnancy. The symptoms of trigeminal neuralgia and its treatment by alcohol injection are well described, but operations on the root of the trigeminal nerve are given little attention. No mention is made of the role of the intravertebral disks in sciatic neuralgia.

In the section on diseases of the spinal cord the treatment of combined system disease is viewed pessimistically and the importance of massive doses of liver extract fails to be recognized. The treatment of neurosyphilis is given in rather general terms. The treatment of myasthenia with prostigmine and similar substances is not mentioned at all.

In the second volume a large and excellent section is devoted to consideration of the diseases of the sympathetic nervous system, although here also surgical implications and results receive little attention. The long chapter on extrapyramidal disease is clearly written, and the disease groups are well characterized.

In the section on diseases of the brain the description of methods of localization is brief. Aphasia is considered on the basis of symptom complexes, and a simple anatomic diagram is given. The subject of encephalitis is well covered, and there is an exceptionally clear account of the clinical course of the separate postinfectious types. The section on histopathology of cerebral tumors is particularly well written and illustrated. The various clinical entities are less thor-

oughly described, and the indications for surgical treatment are extremely brief. Little space is devoted to cerebral abscesses.

In the section on dementia paralytica there is no mention of the use of tryparsamide or of artificial fever. The chapter on head wounds includes many interesting cases from the Spanish Civil War. The subject of electrical injury is considered more fully than usual. The consideration of infantile hydrocephalus is brief and makes little mention of the circulation of the spinal fluid, the coexistence of other congenital defects or the newer forms of surgical treatment, such as operations on the choroid plexus.

Epilepsy is considered among the neuroses, although recent work on electroencephalographic patterns, chemical changes and focal lesions is briefly mentioned. Altogether, this chapter seems rather old fashioned. The remainder of the section on the neuroses is brief and largely descriptive.

These criticisms of details should not be interpreted as reflecting on the value of the book as a whole. In general it gives an excellent account of the practical diagnosis and treatment of the diseases of the nervous system, which is especially notable for its clarity. It would be improved by a bibliography, for though many writers are mentioned, no definite references are given. The authors have evidently drawn from the literature of every civilized country. A preponderance of French articles is noticeable, and illustrates the difficulty of transmitting ideas across oceans, which impairs most medical writing.

Neurosyphilis. By C. Worster-Drought. Price, 10s. 6d. Pp. 214, with illustrations. London: John Bale, Sons & Staples, Ltd., 1940.

This book is intended as a manual for general practitioners, and seems adequate for its purpose. The various forms of neurosyphilis are clearly described in a didactic manner, and with due appreciation of transitional and atypical forms of the disease. A brief account of the pathologic anatomy is given with each entity, and treatment is outlined. The historical aspects of the subject are admirably done, and well documented in the bibliography.

Experienced neurologists may be irked by certain shortcomings of the book. Most of the pathologic descriptions are taken from rather old textbooks. The work of Orr and Rowes is taken at its face value. The use of tryparsamide and its special indications are passed over hastily. The Swift-Ellis treatment is still recommended and illustrated. The prognosis of optic neuritis is given as hopeless, and no therapeutic implications are suggested. The discussion of treatment by artificial fever is inadequate. Only a handful of references (17) to articles appearing in medical journals during the past decade are given, and only 2 of these are to non-British journals. These defects are not serious when one considers that the text is intended for British practitioners.

The book is of a convenient size, well bound and printed in good type. Some of the halftones (for example, figure 9) leave much to be desired, and the graphs are reproduced from typewritten originals.

CORRECTION

In the department of "News and Comment" under the subhead "Quarterly Journal of Studies on Alcohol" in the September issue (ARCH. NEUROL. & PSYCHIAT. **44**:647, 1940), it was erroneously stated that the British journal *Inebriety* has been discontinued. The periodical is still being published.

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